

sponsor. The sponsor verified that the return of medication was 98.0% for Site 152A, 99.3% for Site 152B, and 98.7% for overall return.

Five patients in the Clindoxyl group, 9 patients in the Clindamycin group, 9 patients in the Benzoyl group, and 2 patients in the Vehicle group did not complete the study and thus were considered not valid (non-evaluable) and excluded from the preferred data set. The difference between treatment groups was not significant ($P=0.5$). Four of these patients did not complete the entire treatment period because of protocol violations which included use of excluded concomitant medication during the study (3 patients) and becoming pregnant for 1 patient (152A/085). In addition, 5 patients that completed the study were also considered not valid because of antibiotic use (1 patient in the Vehicle group - 152A/086) and 2 patients in the Clindoxyl group (152A/005 and 152A/074), non-compliant birth control pill use (1 patient in the Clindamycin group - 152A/111), and 1 patient (152A/030) for missing the last 15 applications in the Benzoyl group.

Site	Benzoyl	Clindamycin	Vehicle	Clindoxyl	ALL
152A	33 (94.3)	34 (100)	18 (94.7)	35 (97.2)	120 (96.8)
152B	35 (100)	36 (100)	18 (100)	36 (97.3)	125 (99.2)
ALL	68 (97.1)	70 (100)	36 (97.3)	71 (97.3)	245 (98.0)

Protocol Conduct

There were some deviations from the protocol, such as procedures not done within the time constraints specified in the protocol and concomitant antibiotic usage, which did not cause the patients to be disqualified. Sixteen valid patients deviated from the \pm 5 day schedule variation by 1 to 5 days including 4 patients in the Clindoxyl group, 4 patients in the Clindamycin group, 3 patients in the Benzoyl group, and 5 patients in the Vehicle group ($P=0.2$). Ten valid patients had concomitant short term antibiotic usage which the investigator did not consider as having an effect on acne. Three valid patients had concomitant short term corticosteroid usage which the investigator did not consider as having an effect on acne. One patient in the Clindoxyl group was utilizing a once every other day treatment. These protocol deviations did not affect the interpretation of the study results.

EFFICACY RESULTS OF Study 152

Data Sets Analyzed

Only patients completing the study and compliant with the protocol were considered valid, and their data were included in the preferred data set. All patients with data were included in the intent-to-treat analysis data set (Table 152.4).

Site	Treatment	Preferred Data Set					Intent to Treat Data Set				
		W0	W2	W5	W8	W11	W0	W2	W5	W8	W11
152 A	Benzoyl Peroxide	35	34	35	34	35	40	39	37	36	36
	Clindamycin	34	33	34	34	34	40	37	37	36	35
	Vehicle	19	19	19	19	19	20	20	20	20	20
	Clindoxyl	36	35	36	35	36	40	38	39	37	38
	ALL	124	121	124	122	124	140	134	133	129	129
152B	Benzoyl Peroxide	35	35	35	35	35	40	39	37	36	35
	Clindamycin	36	36	36	36	36	40	39	36	36	36
	Vehicle	18	18	18	18	18	20	20	19	19	18
	Clindoxyl	37	37	37	37	37	40	39	39	38	37
	ALL	126	126	126	126	126	140	137	131	129	126
ALL	Benzoyl Peroxide	70	69	70	69	70	80	78	74	72	71
	Clindamycin	70	69	70	70	70	80	76	73	72	71
	Vehicle	37	37	37	37	37	40	40	39	39	38
	Clindoxyl	73	72	73	72	73	80	77	78	75	75
	ALL	250	247	250	248	250	280	271	264	258	255

The Clindoxyl group had 73 patients, the Clindamycin group had 70 patients, the Benzoyl group had 70 patients, and the Vehicle group had 37 patients in the preferred data set at the completion of treatment at Week 11. The difference between the treatment groups was not significant ($P=0.7$). There were 1 to 2 more patients in each group in the intent-to-treat data set at the completion of treatment (Week 11) than in the preferred data set due to exclusion of five patients. Table 152.5 summarizes patients with data missing or excluded and reasons for exclusion from the preferred data set for each site, each treatment group, and each visit. The Benzoyl group and the Clindamycin group tended to have more missing data than the other groups due to the larger number (9 and 9, respectively) of patient withdrawals (Table 152.1). The amount of excluded data was similar for all groups ($P=0.7$).

Demographic and Baseline Features

The characteristics (sex, race, age, age range, baseline lesion counts, and baseline tolerance scores) of patients in each group of the intent-to-treat data set (Table 152.7) were not significantly different ($P>0.05$).

However, there were highly significant differences between two sites relative to baseline non-inflammatory lesion counts ($P<0.001$). Namely, the mean baseline counts of the non-inflammatory lesions in the Benzoyl, Clindamycin, Vehicle, and Clindoxyl groups were 48.6, 42.9, 51.1, and 58.7 at Site 152A and 24.0, 23.7, 27.6, and 23.8 at Site 152B. Because of the highly significant imbalance in the baseline count of non-inflammatory lesions, the separate efficacy analyses for the two sites

152A and 152B were performed.

The characteristics of the patients in the preferred data set were similar to those of the intent-to-treat data set. The patient population consisted primarily of Caucasian teenagers of either sex.

Site	Treatment ^b	Week 0 Lesion Counts ^a (mean ± s.e.)		Week 0 Local Tolerance Scores (# of patients with mild or moderate scores ^c)		
		Inflammatory	Non-Inflammatory	Erythema	Burning	Peeling
152A	BPO	21.4 ± 1.5	48.6 ± 4.2	1	0	0
	Clindamycin	21.5 ± 1.8	42.8 ± 4.4	0	0	1
	Vehicle	22.6 ± 1.9	51.0 ± 6.3	2	0	0
	Clindoxyl	21.5 ± 1.2	58.6 ± 5.6	0	0	0
	ALL	21.6 ± 0.8	50.2 ± 2.6	3 (2.1%)	0 (0.0%)	1 (0.7%)
152B	BPO	21.2 ± 1.4	24.0 ± 1.6	20	2	0
	Clindamycin	18.4 ± 1.1	23.7 ± 1.6	26	0	0
	Vehicle	20.4 ± 1.8	27.6 ± 2.4	12	2	0
	Clindoxyl	19.8 ± 1.0	23.8 ± 1.3	23	3	0
	ALL	19.9 ± 0.6	24.4 ± 0.8	81 (57.9%)	7 (5.0%)	0 (0.0%)
ALL	BPO	21.3 ± 1.0	36.3 ± 2.6	21	2	0
	Clindamycin	20.0 ± 1.1	33.3 ± 2.6	26	0	1
	Vehicle	21.5 ± 1.3	39.3 ± 3.8	14	2	0
	Clindoxyl	20.7 ± 0.8	41.2 ± 3.5	23	3	0
	ALL	20.8 ± 0.5	37.3 ± 1.6	84 (30.0%)	7 (2.5%)	1 (0.4%)

^a There were no significant differences ($p > 0.05$) between groups, but there were significant differences ($p < 0.0001$) between sites for non-inflammatory lesions

^b BPO = Benzoyl Peroxide. ^c There were no severe scores.

Analysis of Each Efficacy Measure

Efficacy was determined by counting non-inflammatory and inflammatory lesions and grading global improvement throughout the study. There were no treatment by sex, race, or age interactions in any of efficacy analyses, but all analyses of the primary efficacy variables revealed significant ($P < 0.001$) treatment by site interactions. Since this strong treatment by site interaction was evident, the separate analyses of the efficacy measures for each site were performed in addition to the analyses of the combined sites data.

Non-Inflammatory Lesion Counts

As can be seen from Figure 152.1, at Site 152A non-inflammatory lesion counts declined in all groups as time of treatment increased, but at Site 152B non-inflammatory lesion counts were generally constant throughout the study for all

groups. As can be seen from Figure 152.2, the percent reduction in non-inflammatory lesions was greater for the Clindoxyl group than the other groups throughout the study for Site 152A or both sites combined. At Site 152B the Vehicle group had the greatest percent reduction.

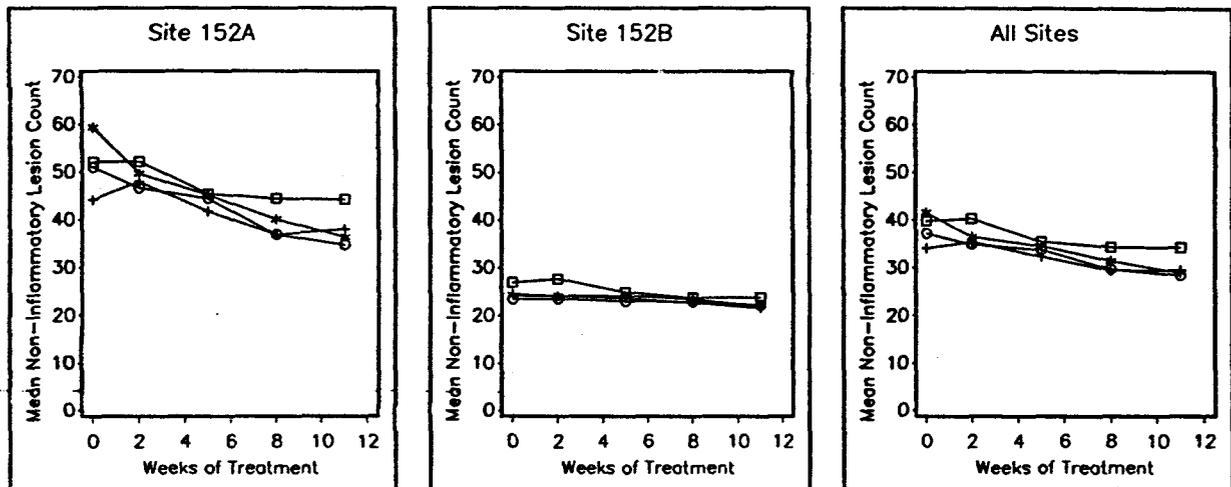


Figure 152.1: Mean non-inflammatory lesion count in the preferred data set by site and all sites combined after 0-11 weeks of treatment with Benzoyl (o), Clindamycin (+), Vehicle (□), or Clindoxyl (*).

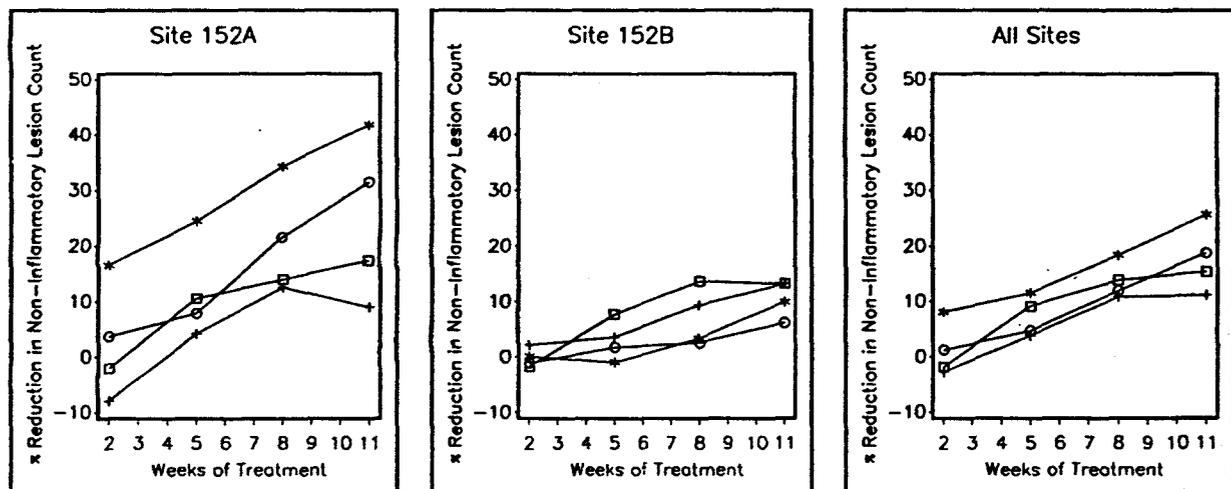


Figure 152.2: Mean percent reduction in non-inflammatory lesion count in the preferred data set by site and all sites combined after 2-11 weeks of treatment with Benzoyl (o), Clindamycin (+), Vehicle (□), or Clindoxyl (*).

At Site 152A, the mean percent reduction at 11 weeks was 41.8 for the Clindoxyl group, 31.5 for the Benzoyl group, 9.0 for the Clindamycin group and 17.4 for the Vehicle group (Table 152.8). As can be seen from Tables 152.8, and 152.9, at Site 152A, the Clindoxyl group had a significantly ($P \leq 0.01$) greater percent reduction in non-inflammatory lesions at Week 11 than the Clindamycin or Vehicle groups. Compared to Benzoyl, Clindoxyl produced a numerically greater percent reduction in

non-inflammatory lesions at Week 11 ($P=0.19$).

At Site 152.B, Vehicle produced numerically greater percent reduction than Clindoxyl ($P=0.37$), Benzoyl ($P=0.056$), and Clindamycin ($P=1.0$) at Week 11. Vehicle was consistently better than active treatments throughout the study at Site 152B.

Week	Statistic ¹	Site	Benzoyl Peroxide	Clindamycin	Vehicle	Clindoxyl
0	Mean Count	152A	51.0	44.2	52.1	59.4
		152B	23.4	24.5	26.9	24.2
		ALL	37.2	34.1	39.8	41.6
2	Mean Reduction	152A	3.4	-3.2	-0.1	9.0 ^{v,b,c}
		152B	-0.2	0.4	-0.8	0.1
		ALL	1.6	-1.3	-0.4	4.4 ^{v,b,c}
	Mean % Reduction	152A	3.7	-7.9	-2.0	16.5 ^{v,b,c}
		152B	-1.1	2.2	-1.7	0.2
		ALL	1.3	-2.7	-1.8	8.1 ^{v,b,c}
5	Mean Reduction	152A	6.5	2.4	6.6	14.2 ^{b,c}
		152B	0.3 ^v	0.9	2.0	-0.0 ^v
		ALL	3.4	1.6	4.4	7.0 ^{b,c}
	Mean % Reduction	152A	7.9	4.2	10.6	24.5 ^{b,c}
		152B	1.8	3.6	7.7	-0.9 ^v
		ALL	4.8	3.9	9.2	11.6 ^{b,c}
8	Mean Reduction	152A	11.7	7.4	7.5	20.0 ^{v,c}
		152B	0.5 ^v	2.0	3.3	0.8 ^{v,c}
		ALL	6.0	4.6	5.5	10.1 ^c
	Mean % Reduction	152A	21.6	12.6	14.0	34.3 ^{v,c}
		152B	2.6 ^v	9.4	13.7	3.4 ^{v,c}
		ALL	12.0	10.9	13.9	18.4
11	Mean Reduction	152A	16.2	6.2	7.8	23.0 ^{v,c}
		152B	1.2 ^v	2.9	3.2	2.2
		ALL	8.7	4.5	5.5	12.5 ^{v,c}
	Mean % Reduction	152A	31.5	9.0	17.4	41.8 ^{v,c}
		152B	6.2	13.3	13.3	10.0
		ALL	18.8	11.2	15.4	25.7 ^{v,c}
ITT-LOCF	Mean Reduction	152A	13.9	6.3	8.5	22.0 ^{v,c}
		152B	0.9 ^v	2.6	3.2	1.8
		ALL	7.4	4.5	5.9	11.9 ^{v,b,c}
	Mean % Reduction	152A	27.2	9.4	20.0	39.9 ^{v,c}
		152B	5.2 ^v	12.0	13.1	8.1
		ALL	16.2	10.7	16.5	24.0 ^c

¹ Reduction = baseline count - count at a later week
^{v,c,b} Significantly different from vehicle (v), clindamycin (c), or benzoyl peroxide (b), $p < 0.05$ (Table 152.9)

TABLE 152.9
Percent Reduction at Week 11 of Non-Inflammatory Lesion Counts in Study 152
Results of Statistical Analyses in the Preferred Data Set*

Treatment Comparison			Least Square Mean			
First	Second	Site	First	Second	Difference	p-Value
Clindoxyl	Vehicle	152A	41.8	17.4	24.4	0.010
		152B	10.0	13.3	-3.3	0.371
		ALL	25.9	15.3	10.5	0.037
Clindoxyl	Benzoyl Peroxide	152A	41.8	31.5	10.3	0.191
		152B	10.0	6.2	3.8	0.202
		ALL	25.9	18.8	7.0	0.091
Clindoxyl	Clindamycin	152A	41.8	9.0	32.8	0.000
		152B	10.0	13.3	-3.3	0.271
		ALL	25.9	11.1	14.7	0.000
Benzoyl Peroxide	Vehicle	152A	31.5	17.4	14.1	0.135
		152B	6.2	13.3	-7.1	0.056
		ALL	18.8	15.3	3.5	0.490
Clindamycin	Vehicle	152A	9.0	17.4	-8.4	0.373
		152B	13.3	13.3	0.0	0.998
		ALL	11.1	15.3	-4.2	0.406

* Site*treatment interaction was significant (p=0.0001).
Reduction = baseline count - count at a later week.

Inflammatory Lesion Counts

As can be seen from Figure 152.3, inflammatory lesion counts declined in all groups as time of treatment increased for both sites. As can be seen from Figure 152.4, the percent reduction in inflammatory lesions was consistently greater for the Clindoxyl group than the other groups throughout the study for Site 152A and both sites combined (Figure 152.4).

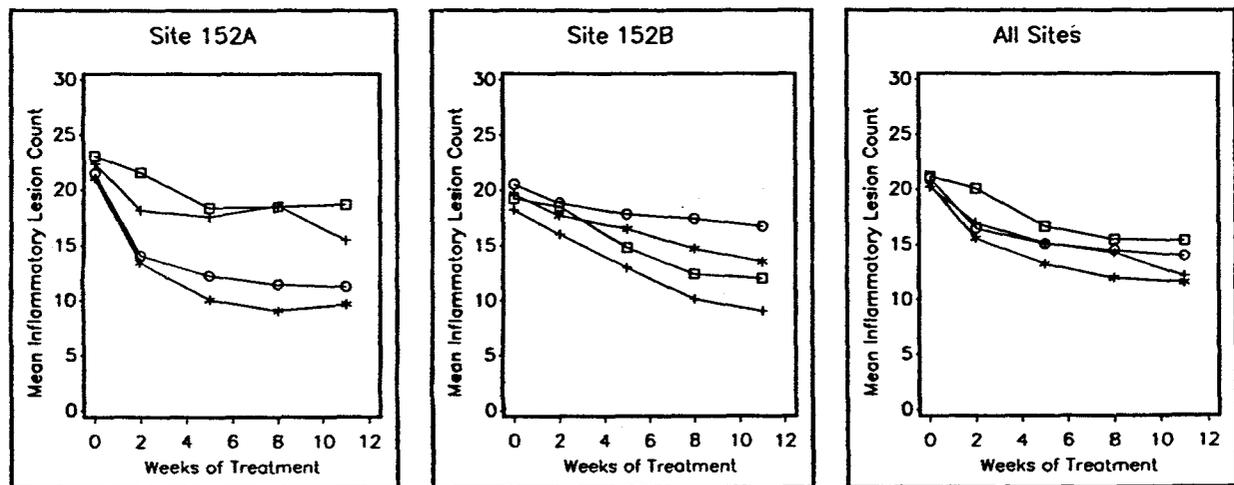


Figure 152.3: Mean inflammatory lesion count in the preferred data set by site and all sites combined after 0-11 weeks of treatment with Benzoyl (o), Clindamycin (+), Vehicle (□), or Clindoxyl (*).

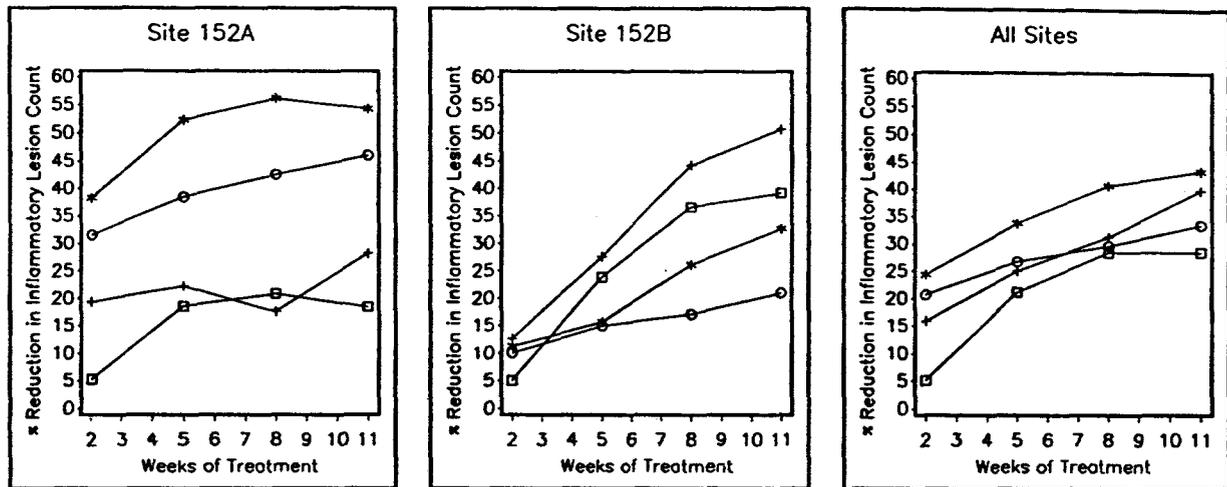


Figure 152.4: Mean percent reduction in inflammatory lesion count in the preferred data set by site and all sites combined after 2-11 weeks of treatment with Benzoyl (o), Clindamycin (+), Vehicle (□), or Clindoxyl (*).

At Site 152A the mean percent reduction at 11 weeks was 54.4 for the Clindoxyl group, 46.1 for the Benzoyl group, 28.2 for the Clindamycin group, and 18.5 for the Vehicle group (Table 152.10). As can be seen from Tables 152.10 and 152.11, at Site 152A, the Clindoxyl group had a significantly greater percent reduction than the Clindamycin and Vehicle groups at Week 11 ($P \leq 0.019$). Compared to Benzoyl, Clindoxyl had a numerically greater percent reduction in inflammatory lesions at Week 11 ($P = 0.448$).

At site 152.B, as can be seen from Tables 152.10 and 152.11, the mean percent reduction at 11 weeks was substantially higher for the Clindamycin group (50.8) and the Vehicle group (39.2) and lower for the Clindoxyl group (32.7) and the Benzoyl group (21.0). Compared to Benzoyl, the Clindoxyl group had a significantly ($P = 0.048$) greater percent reduction at Week 11 (Tables 152.10 and 152.11). However, the Clindoxyl group had a significantly lower percent reduction than the Clindamycin group at Week 11 ($P = 0.002$). After combining sites, most differences disappear except for the marginally significantly greater percent reduction in the Clindoxyl group than the Vehicle group at Week 11 ($P = 0.051$). When the same comparisons were made with the intent-to-treat data set, similar results were obtained.

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Week	Statistic ¹	Site	Benzoyl Peroxide	Clindamycin	Vehicle	Clindoxyl
0	Mean Count	152A	21.5	22.4	23.1	21.1
		152B	20.5	18.2	19.2	19.6
		ALL	21.0	20.2	21.2	20.4
2	Mean Reduction	152A	7.3 ^v	4.4	1.5	7.8 ^{v,c}
		152B	1.7	2.3 ^v	0.7	2.0 ^v
		ALL	4.4 ^v	3.3 ^v	1.1	4.8 ^v
	Mean % Reduction	152A	31.6 ^v	19.4	5.3	38.3 ^{v,c}
		152B	10.1	12.7 ^v	5.1	11.3
		ALL	20.7 ^v	15.9 ^v	5.2	24.4 ^{v,c}
5	Mean Reduction	152A	9.2	4.8	4.7	11.1 ^{v,c}
		152B	2.7	5.2	4.3	3.2 ^c
		ALL	5.9	5.0	4.5	7.1 ^{v,c}
	Mean % Reduction	152A	38.5	22.3	18.6	52.4 ^{v,c}
		152B	15.0	27.6	23.9	15.7 ^c
		ALL	26.8	25.1	21.2	33.8 ^v
8	Mean Reduction	152A	9.6	3.8	4.6	11.9 ^{v,c}
		152B	3.1 ^v	8.1	6.8	4.9 ^c
		ALL	6.3	6.0	5.6	8.3
	Mean % Reduction	152A	42.6	17.6	20.9	56.2 ^{v,c}
		152B	17.1 ^v	44.3	36.6	26.1 ^c
		ALL	29.7	31.3	28.5	40.7
11	Mean Reduction	152A	10.3 ^v	6.9	4.4	11.5 ^{v,c}
		152B	3.7 ^v	9.2	7.2	6.1 ^{b,c}
		ALL	7.0	8.1	5.8	8.8 ^v
	Mean % Reduction	152A	46.1 ^v	28.2	18.5	54.4 ^{v,c}
		152B	21.0 ^v	50.8	39.2	32.7 ^{b,c}
		ALL	33.5	39.8	28.6	43.4
ITT-LOCF	Mean Reduction	152A	10.0 ^v	6.5	4.8	11.1 ^{v,c}
		152B	3.4 ^v	8.6	6.7	5.7 ^{b,c}
		ALL	6.7	7.5	5.8	8.4
	Mean % Reduction	152A	44.1	28.0	21.9	52.6 ^{v,c}
		152B	19.2 ^v	47.1	36.6	30.7 ^{b,c}
		ALL	31.6	37.5	29.2	41.7

¹ Reduction = baseline count - count at a later week (v,c,b Significantly different from vehicle (v), clindamycin (c), or benzoyl peroxide (b), p < 0.05 (Table 152.11, based on valid patients, LOCF).

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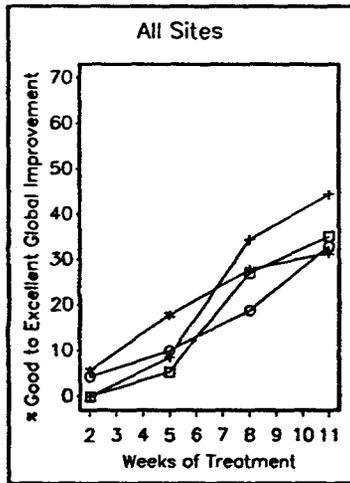
Treatment Comparison			Least Square Mean			
First	Second	Site	First	Second	Difference	p-Value
Clindoxyl	Vehicle	152A	54.4	18.5	35.9	0.007
		152B	32.7	39.2	-6.6	0.360
		ALL	43.5	28.9	14.7	0.051
Clindoxyl	Benzoyl Peroxide	152A	54.4	46.1	8.3	0.448
		152B	32.7	21.0	11.7	0.048
		ALL	43.5	33.5	10.0	0.107
Clindoxyl	Clindamycin	152A	54.4	28.2	26.2	0.019
		152B	32.7	50.8	-18.2	0.002
		ALL	43.5	39.5	4.0	0.517
Benzoyl Peroxide	Vehicle	152A	46.1	18.5	27.6	0.038
		152B	21.0	39.2	-18.3	0.013
		ALL	33.5	28.9	4.7	0.537
Clindamycin	Vehicle	152A	28.2	18.5	9.7	0.464
		152B	50.8	39.2	11.6	0.109
		ALL	39.5	28.9	10.7	0.158

^a Site * treatment interaction was significant (p=0.0001).
Reduction = baseline count - count at a later week.

Global Improvement Scores

As can be seen from Figure 152.5, at Site 152A, the percentage of patients with good to excellent global improvement was consistently greater for the Clindoxyl group than the other groups throughout the study. At Site 152A the percentage of patients with good to excellent global improvement at 11 weeks was 47.2 for the Clindoxyl group, 42.9 for the Benzoyl group, 17.6 for the Clindamycin group, and 26.3 for the Vehicle group (Table 152.12). As can be seen from Table 152.13, at Site 152A, the Clindoxyl group had a numerically greater proportion of patients with good to excellent global improvement than the Vehicle or Clindamycin groups but did not reach statistical significance ($P \leq 0.3$).

As can be seen from Figure 152.5, at Site 152B, the percentage of patients with good to excellent global improvement was consistently greater for the Clindamycin group than the other groups throughout the study. At Site 152B the percentage of patients with good to excellent global improvement at 11 weeks were substantially higher for the Clindamycin group (69.4) and the Vehicle group (44.4) and lower for the Benzoyl group (22.9) and the Clindoxyl group (16.2). When both sites were combined, the rank order of Site 152B was maintained (Table 12). At Week 11, the Clindamycin group had significantly greater proportions of patients with good to excellent global improvement compared to the Clindoxyl group at Site 152B (Table 152.13).



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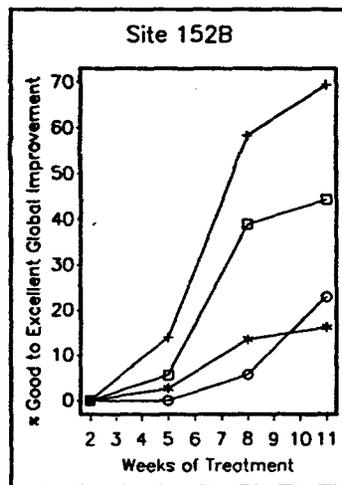
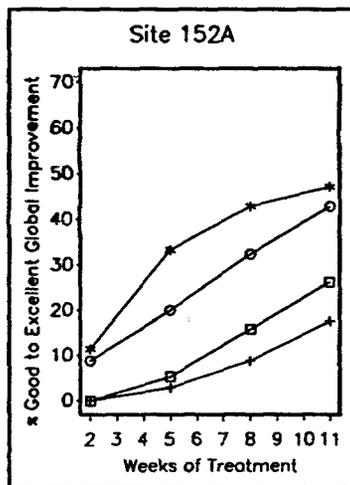


Figure 152.5: Percent of patients with good to excellent global improvement in the preferred data set by site and all sites combined after 2-11 weeks of treatment Benzoyl (o), Clindamycin (+), Vehicle (□), or Clindoxyl (*).

TABLE 152.12
Patients with Good to Excellent Global Improvement in the Preferred Data Set of Study 152

Week	Site	Benzoyl Peroxide	Clindamycin	Vehicle	Clindoxyl
2	152A	3 (8.8%)	0 (0.0%)	0 (0.0%)	4 (11.4%)
	152B	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	ALL	3 (4.3%)	0 (0.0%)	0 (0.0%)	4 (5.6%)
5	152A	7 (20.0%)	1 (2.9%)	1 (5.3%)	12 (33.3%)
	152B	0 (0.0%)	5 (13.9%)	1 (5.6%)	1 (2.7%)
	ALL	7 (10.0%)	6 (8.6%)	2 (5.4%)	13 (17.8%)
8	152A	11 (32.4%)	3 (8.8%)	3 (15.8%)	15 (42.9%)
	152B	2 (5.7%)	21 (58.3%)	7 (38.9%)	5 (13.5%)
	ALL	13 (18.8%)	24 (34.3%)	10 (27.0%)	20 (27.8%)
11	152A	15 (42.9%)	6 (17.6%)	5 (26.3%)	17 (47.2%)
	152B	8 (22.9%)	25 (69.4%)	8 (44.4%)	6 (16.2%)
	ALL	23 (32.9%)	31 (44.3%)	13 (35.1%)	23 (31.5%)
ITT-LOCF ^b	152A	16 (40.0%)	7 (17.5%)	6 (30.0%)	17 (42.5%)
	152B	8 (20.0%)	25 (62.5%)	8 (40.0%)	6 (15.0%)
	ALL	24 (30.0%)	32 (40.0%)	14 (35.0%)	23 (28.8%)

^b Endpoint includes all patients with last observation carried forward.

Treatment Comparison			Proportion		Estimated Odds Ratio ^b	p-Value ^b
First	Second	Site	First	Second		
Clindoxyl	Vehicle	152A	0.47	0.26	2.51	0.340
		152B	0.16	0.44	0.24	0.119
		ALL	0.32	0.35	0.78	0.577
Clindoxyl	Benzoyl Peroxide	152A	0.47	0.43	1.19	0.821
		152B	0.16	0.23	0.65	0.602
		ALL	0.32	0.33	0.88	0.745
Clindoxyl	Clindamycin	152A	0.47	0.18	4.18	0.095
		152B	0.16	0.69	0.09	0.002
		ALL	0.32	0.44	0.60	0.197
Benzoyl Peroxide	Vehicle	152A	0.43	0.26	2.10	0.234
		152B	0.23	0.44	0.37	0.110
		ALL	0.33	0.35	0.88	0.775
Clindamycin	Vehicle	152A	0.18	0.26	0.60	0.458
		152B	0.69	0.44	2.84	0.080
		ALL	0.44	0.35	1.31	0.558

^a Site*treatment interaction was significant (p<0.001)
^b Obtained from logistic regression

CONCLUSIONS ON EFFICACY IN Study 152

The percent change from baseline of non-inflammatory and inflammatory lesions and success with global improvement scores at Week 11 were considered primary efficacy variables. In general the relative responses to treatment as measured by the primary efficacy variables for Site 152A were similar to the relative responses observed at 5 other sites in Studies 150 and 151, i.e. that treatment responses were best with Clindoxyl, followed by Benzoyl, Clindamycin, and Vehicle. However relative responses observed at Site 152B did not follow this ranking as benzoyl peroxide containing products (Benzoyl and Clindoxyl) showed poorer effectiveness than either Clindamycin or Vehicle. Since the treatment by site interaction was highly statistically significant ($P < 0.001$), the analyses of the efficacy measures was performed separately for each site in addition to the analyses of the combined sites data.

At Site 152A, the Clindoxyl group had significantly ($P \leq 0.019$) greater percent reductions in inflammatory and non-inflammatory lesions than the Clindamycin and the Vehicle groups at 11 weeks. Relative to global assessment, the Clindoxyl group had numerically (but not significantly) greater proportion of patients (47%) with good to excellent global improvement at Week 11 than the Clindamycin group (18%) or the Vehicle group (26%) with $P \geq 0.3$.

At Site 152B, the Clindoxyl group had significantly ($P < 0.048$) greater percent reductions in inflammatory lesions than the Benzoyl group but these same percent reductions were significantly lower than the Clindamycin group ($P < 0.002$). This poor response of the Clindoxyl group (and the Benzoyl group) was apparent when comparing the proportions of patients with good to excellent global improvement for

the Clindoxyl group (16%) and the Benzoyl group (23%) to the Clindamycin group (69%) and the Vehicle group (44%). The Clindoxyl group had a significantly ($P < 0.002$) lower proportion of patients with good to excellent global improvement at 11 weeks than the Clindamycin group. In addition the Vehicle group had significantly ($P = 0.013$) greater percent reduction in inflammatory lesions at 11 weeks than the Benzoyl group. The poor performance of the two benzoyl peroxide containing products at this site should be investigated since it is not consistent with the recognized effectiveness of benzoyl peroxide in treating acne vulgaris. Site 152B should be a candidate for DSI inspection.

Combining the data of the two sites usually eliminated any differences between groups with the exception of non-inflammatory lesion percent reduction. Relative to the percent reduction at Week 11 of non-inflammatory lesion counts, the Clindoxyl group had a significantly greater response than the Clindamycin and Vehicle groups ($P \leq 0.037$) and approached a significant difference compared to the Benzoyl group ($P = 0.09$). All of the primary efficacy variable analyses showed significant treatment by site interaction ($P < 0.001$).

Efficacy results were different at sites 152A and 152B. At site 152A, Clindoxyl produced a significantly greater ($P < 0.019$) percent reduction at Week 11 of inflammatory and non-inflammatory lesion counts than the Clindamycin, or Vehicle. Compared to Benzoyl, Clindoxyl produced numerically (but not significantly) greater reduction of non-inflammatory and inflammatory lesions ($P \leq 0.5$). At site 152A, Clindoxyl had a numerically (but not significantly, $P \geq 0.3$) greater proportion of patients with good to excellent global improvement at Week 11 than Clindamycin or Vehicle.

At site 152B, both Clindoxyl and Benzoyl produced very poor results compared with Clindamycin and Vehicle. Since Benzoyl performed unusually poorly at site 152B, the study at site 152B was considered a failed trial and ignored in the analysis. Site 152B should be a candidate for DSI inspection.

The ITT-LOCF analysis supported the results of the preferred analysis.

ANALYSIS OF COMBINED SITES 150 AND 152A

Since Study 150 had only one center, data from Study 150 and site 152A were combined. Results of combined analysis of sites 150 and 152A are shown in Tables 152.A and 152.B. Clindoxyl treatment was significantly ($P \leq 0.001$) more effective than Vehicle or Clindamycin treatments relative to the percent reduction of inflammatory or non-inflammatory lesions and in global improvement. Clindoxyl also was significantly ($P \leq 0.037$) better than Benzoyl with the exception of the percent reduction of non-inflammatory lesions ($P = 0.1$).

Table 152.A Results of combined analysis of sites 150 and 152A Global improvement and percent reductions of lesion counts. Valid patients only.				
Measure (Week 11)	Clindoxyl	Benzoyl	Clindamycin	Vehicle
Number of patients	64	59	63	46
Percent reduction of lesion counts				
Inflammatory	60%	43%	31%	19%
Non-inflammatory	34%	23%	2%	2%
Global improvement				
Success (score 3 or 4)	62%	42%	27%	20%

Table 152.B P-values in the combined analysis of sites 150 and 152A			
Comparison	Inflammatory lesions	Non-inflammatory lesions	Success with global improvement
Clindoxyl vs. Benzoyl	0.037	0.16	0.036
Clindoxyl vs. Clindamycin	0.001	0.000	0.000
Clindoxyl vs. Vehicle	0.000	0.000	0.000
Benzoyl vs. Vehicle	0.010	0.008	0.020
Clindamycin vs. Vehicle	0.168	0.942	0.435

CONCLUSIONS ON EFFICACY IN COMBINED SITES 150 AND 152A.

Analysis of the combined data for sites 150 and 152A supports the sponsor's claim that once daily use of Clindoxyl is effective for treatment acne vulgaris. Clindoxyl treatment was significantly ($P \leq 0.001$) more effective than Vehicle or Clindamycin treatments relative to the percent reduction of inflammatory or non-inflammatory lesions and in global improvement. Clindoxyl also was significantly ($P \leq 0.037$) better

than Benzoyl with the exception of the percent reduction of non-inflammatory lesions ($P=0.1$).

SAFETY

SAFETY RESULTS OF Study 150

Extent of Exposure

The extent of exposure to study medications of all patients that entered Study 150 is summarized in Table 150.12. Most patients (83.3%) had an exposure (71-84 applications) which approximated the protocol prescribed application dose of once daily for 11 weeks. Exposure was similar for all treatment groups except the Clindamycin group which tended to have somewhat higher exposure. Lower extent of exposure was usually due to discontinued study participation. Seven percent of patients that completed the study had a lower exposure (57 to 70 applications) due to missed applications. One patient (150/120) had 36 applications due to using the Vehicle every other day for most of the study.

# of Applications	Distribution of Patients by # of Applications (planned exposure 77 applications in 77 days)				
	Benzoyl Peroxide	Clindamycin	Vehicle	Clindoxyl	ALL
0 to 14*	3 (10.0%)	1 (3.3%)	2 (6.7%)	1 (3.3%)	7 (5.8%)
15 to 28	0	0	0	0	0
29 to 42	1 (3.3%)	0	1 (3.3%)	1 (3.3%)	3 (2.5%)
43 to 56	1 (3.3%)	0	1 (3.3%)	0	2 (1.7%)
57 to 70	2 (6.7%)	1 (3.3%)	2 (6.7%)	3 (10.0%)	8 (6.7%)
71 to 84	23 (76.7%)	28 (93.3%)	24 (80.0%)	25 (83.3%)	100 (83.3%)
> 84	0	0	0	0	0

* Includes unknowns.

Adverse Events

A total of 31 adverse events were reported on 26 patients during the study (Table 150.13). Analysis of the frequency of patients with reported adverse events demonstrated no significant differences between treatment groups ($P>0.05$). The Clindoxyl group had 8 (26.7%) patients that reported a total of 11 adverse events (Table 150.13). All of the 11 adverse events that were reported were considered to be of mild intensity and had no relationship to the study medication. Final outcomes

were reported as recovered except for 1 patient (150/094) that had an outcome reported as residual. There was no change in study medication usage for any of the 8 Clindoxyl patients that reported adverse events.

	Clindoxyl	Clindamycin	Benzoyl Peroxide	Vehicle	All
# of patients	8 (26.7%)	7 (23.3%)	5 (16.7%)	6 (20.0%)	26 (21.7%)
# of events	11	8	5	7	31

* Reoccurring events were counted once. There was no significant difference between groups ($p > 0.05$, Fisher's exact test).

Additional Safety Observations

The tolerance of the study medication was determined by physician evaluation of erythema, peeling, and burning throughout the study and of overall tolerance at the last visit for each patient. All four treatments were well tolerated, except for occasional mild or rarely moderate erythema, peeling, burning, or pruritus. Local tolerance scores throughout the study were compared to baseline scores to compare the frequency of treatment emergent signs and symptoms in the four treatment groups (Table 150.14). There were no significant differences between the four treatment groups for change from baseline of signs and symptoms. Most treatment emergent signs and symptoms were modest and involved a single grade worsening (i.e. absent to mild or mild to moderate).

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ON ORIGINAL**

Signs and Symptoms	Treatment	Number of Patients with Worsening Score				
		Week 2	Week 5	Week 8	Week 11	Any
Erythema	Clindoxyl	2 (8.3%)	1 (3.4%)	1 (3.6%)	1 (3.6%)	3 (10.0%)
	Clindamycin	1 (3.6%)	0	0	0	1 (3.3%)
	Benzoyl Peroxide	4 (14.3%)	3 (11.5%)	1 (3.8%)	2 (8.3%)	7 (23.3%)
	Vehicle	3 (11.1%)	4 (14.8%)	1 (3.6%)	2 (7.4%)	6 (20.7%)
Peeling	Clindoxyl	6 (25.0%)	4 (13.8%)	3 (10.7%)	1 (3.6%)	10 (33.3%)
	Clindamycin	1 (3.6%)	2 (7.4%)	1 (3.4%)	0	3 (10.0%)
	Benzoyl Peroxide	2 (7.1%)	2 (7.7%)	2 (7.7%)	1 (4.2%)	6 (20.0%)
	Vehicle	5 (18.5%)	3 (11.1%)	0	0	8 (27.6%)
Burning	Clindoxyl	0	0	0	0	0
	Clindamycin	0	0	0	0	0
	Benzoyl Peroxide	0	0	0	0	0
	Vehicle	0	1 (3.7%)	0	0	1 (3.4%)

* There were no significant differences between groups for any worsening when analyzed by Fisher's exact test ($p > 0.05$).

Treatment	Poor (0)	Fair (1)	Good (2)	Excellent (3)
Clindoxyl	0	0	0	30 (100%)
Clindamycin	0	0	0	30 (100%)
Benzoyl Peroxide	0	0	1 (3.3%)	29 (96.7%)
Vehicle	0	0	0	29 (100%)

There was no significant difference between treatments when analyzed by Fisher's exact test ($p > 0.05$).

Analysis of the distribution of patients by overall tolerance score, the primary safety variable, demonstrated no significant differences ($P > 0.05$) between the four treatment groups (Table 150.15). All but 1 patient had excellent tolerance and even that patient (150/084) had good tolerance.

CONCLUSIONS ON SAFETY IN Study 150

There were no significant differences between treatment groups in Study 150 relative to overall tolerance scores ($P > 0.05$). All patients except one patient in the Benzoyl group had excellent overall tolerance.

There were no significant differences between treatment groups relative to treatment emergent signs and symptoms or relative to the incidence of adverse events ($P > 0.05$). Only one adverse event (mild paraesthesia) was related to treatment (Vehicle).

SAFETY RESULTS OF Study 151Extent of Exposure

The extent of exposure to study medications of all patients that entered the study is summarized in Table 151.14. Most patients (78.4%) had an exposure (71-84 applications) which approximated the protocol prescribed application dose of once daily for 11 weeks. Exposure was similar for all treatment groups. Lower extent of exposure was usually due to discontinued study participation. Some patients (16) that completed the study had somewhat lower exposure (57 to 70 applications) due to missed applications (12 patients), an early final visit (3 patients) or using the wrong study medication (1 patient). One patient (151D/52) had 88 applications due to a late final visit. Another patient (151B/26) had 90 applications due to two weeks of twice daily treatment.

# of Applications	Distribution of Patients by # of Applications (planned exposure 77 applications in 77 days)				
	Benzoyl	Clindamyc in	Vehicle	Clindoxyl	ALL
0 to 14*	4 (5.1%)	12 (15.4%)	5 (12.8%)	5 (6.4%)	26 (9.5%)
15 to 28	0	1 (1.3%)	0	0	1 (0.4%)
29 to 42	2 (2.6%)	2 (2.6%)	2 (5.1%)	3 (3.8%)	9 (3.3%)
43 to 56	2 (2.6%)	2 (2.6%)	0	1 (1.3%)	5 (1.8%)
57 to 70	5 (6.4%)	2 (2.6%)	1 (2.6%)	8 (10.3%)	16 (5.9%)
71 to 84	65 (83.3%)	58 (74.4%)	30 (76.9%)	61 (78.2%)	214 (78.4%)
> 84	0	1 (1.3%)	1 (2.6%)	0	2 (0.7%)

* Includes unknowns.

Adverse Events

A total of 153 adverse events were reported on 113 patients during the study (Table 151.15). Analysis of the frequency of patients with reported adverse events demonstrated no significant difference ($P > 0.05$) between treatment groups.

Treatment	# of patients	# of events ^b
Benzoyl Peroxide	33 (42.3%)	43
Clindamycin	32 (41.0%)	38
Vehicle	14 (35.9%)	23
Clindoxyl	34 (43.6%)	49
ALL	113 (41.4%)	153

^a There was no significant difference between treatment groups when analyzed by Fisher's exact test, $p > 0.05$
^b Reoccurring events were counted once.

The Clindoxyl group had 34 (43.6%) patients that reported a total of 49 adverse events (Table 151.15). Only 1 of the 49 adverse events that were reported had a relationship to the study medication.

Additional Safety Observations

The tolerance of the study medication was determined by physician evaluation of erythema, peeling, and burning throughout the study and of overall tolerance at the last visit for each patient. All four treatments were well tolerated, except for occasional mild or rarely moderate erythema, peeling, burning, dryness, or pruritus. Local tolerance scores throughout the study were compared to baseline scores to compare the frequency of treatment emergent signs and symptoms in the four treatment groups (Table 151.16). There were no significant differences between the four treatment groups for change from baseline of signs and symptoms except for peeling where the Benzoyl and Clindoxyl groups had a significantly higher incidence in worsening peeling scores. Most treatment emergent signs and symptoms were modest and involved a single grade worsening (i.e. absent to mild or mild to moderate).

Analysis of the distribution of patients by overall tolerance score, the primary safety variable, demonstrated no significant differences ($P > 0.05$) between the four treatment groups (Table 151.17). Approximately 92% of the patients in each group had excellent tolerance with the remainder having good tolerance except for 1 patient in both the Clindamycin and Vehicle groups.

TABLE 151.16 Local Tolerance (Change from Baseline of Signs and Symptoms) in Study 151						
Signs and Symptoms	Treatment	Number of Patients with Worsening Score				
		Week 2	Week 5	Week 8	Week 11	Any*
Erythema	Benzoyl	4(5.2%)	5(6.9%)	3(4.5%)	2(2.9%)	8(10.4%)
	Clindamycin	3(4.2%)	2(3.0%)	1(1.7%)	2(3.3%)	6(8.3%)
	Vehicle	0	0	0	1(3.1%)	1(2.7%)
	Clindoxyl	2(2.6%)	5(7.1%)	2(3.0%)	1(1.4%)	5(6.5%)
Peeling*	Benzoyl	8(10.4%)	12(16.7%)	9(13.4%)	5(7.1%)	16(20.8%)
	Clindamycin	2(2.8%)	4(6.1%)	3(5.0%)	3(5.0%)	5(6.9%)
	Vehicle	0	1(2.9%)	1(3.0%)	1(3.1%)	2(5.4%)
	Clindoxyl	8(10.4%)	8(11.4%)	6(9.1%)	3(4.4%)	14(18.2%)
Burning	Benzoyl	0	1(1.4%)	0	0	1(1.3%)
	Clindamycin	0	0	0	0	0
	Vehicle	0	0	0	0	0
	Clindoxyl	1(1.3%)	0	1(1.5%)	0	2(2.6%)
Dryness	Benzoyl	4(5.2%)	5(6.9%)	3(4.5%)	4(5.7%)	8(10.4%)
	Clindamycin	4(5.6%)	4(6.1%)	1(1.7%)	1(1.7%)	6(8.3%)
	Vehicle	1(2.7%)	2(5.9%)	1(3.0%)	1(3.1%)	2(5.4%)
	Clindoxyl	3(3.9%)	4(5.7%)	5(7.6%)	4(5.8%)	9(11.7%)

* A significance difference was seen in the distribution of any worsening of peeling when analyzed by Fisher's exact test ($p=0.02$). There were no significant differences seen for any worsening of erythema, burning, or dryness ($p>0.05$)

TABLE 151.17 Distribution of Patients by Overall Tolerance Score* in Study 151				
Treatment	Poor (0)	Fair (1)	Good (2)	Excellent (3)
Benzoyl Peroxide	0	0	6 (7.8%)	71 (92.2%)
Clindamycin	0	1 (1.4%)	4 (5.6%)	67 (93.1%)
Vehicle	0	1 (2.7%)	2 (5.4%)	34 (91.9%)
Clindoxyl	0	0	6 (7.8%)	71 (92.2%)

* There was no significant difference between treatment groups ($p>0.05$) when analyzed by Fisher's exact test

CONCLUSIONS ON SAFETY IN Study 151

Overall tolerance was identified in the protocol as the primary safety variable. There were no significant ($P > 0.05$) differences between treatment groups relative to overall tolerance scores. All patients except 1 patient in each of the Clindamycin and Vehicle groups had good to excellent overall tolerance. About 92% of the patients in each group had excellent tolerance.

There were no significant differences ($P > 0.05$) between treatment groups relative to treatment emergent signs and symptoms except for peeling where the Benzoyl and Clindoxyl groups had a significantly higher incidence (20%) in worsening peeling scores. In general emergent peeling was more frequent at the earlier evaluations (weeks 2, 5, and 8) for these 2 groups. Little or no emergent burning or pruritus was observed, but some patients (6-12%) had emergent erythema and dryness in all active groups. Most treatment emergent signs and symptoms involved a modest (1 grade) worsening. Five patients had a substantial (> 1 grade) worsening of pruritus, dryness, or peeling but only two of these patients (dryness and peeling) were in the Clindoxyl group. Adverse events were reported by 34 (44%) patients in the Clindoxyl group, 32 (41%) patients in the Clindamycin group, 33 (42%) patients in the Benzoyl group, and 14 (36%) patients in the Vehicle group. There were no significant differences ($P > 0.05$) between treatments relative to the occurrence of adverse events. Only 1 patient had an adverse event (mild paraesthesia) which was definitely related to Clindoxyl treatment, but this event only occurred on the initial day of application.

There was no significant difference ($P > 0.05$) between treatment groups relative to overall tolerance score, occurrence of adverse events, and treatment emergent signs and symptoms except for peeling where the Benzoyl and Clindoxyl groups had a significantly higher incidence (20%) in worsening peeling scores ($P = 0.02$). Only one adverse event (paraesthesia) was related to Clindoxyl treatment.

SAFETY RESULTS OF Study 152

Extent of Exposure

The extent of exposure to study medications of all patients that entered Study 152 is summarized in Table 152.14. Most patients (88.2%) had an exposure (71-84 applications) which was close to the protocol prescribed application dose of once daily for 11 weeks. Exposure was similar for all treatment groups. Lower extent of exposure was usually due to discontinued study participation. Some patients (8) that completed the study had somewhat lower exposure (57 to 70 applications) due to missed applications (5 patients) or an early final visit (3 patients). One patient (152A/124) had 86 applications due to a late final visit. Another patient (152B/041) had 31 applications due to missed applications and once every other day treatment.

Distribution of Patients by # of Applications (planned exposure 77 applications in 77 days)					
# of Applications	Benzoyl Peroxide	Clindamycin	Vehicle	Clindoxyl	ALL
0 to 14*	4 (5.0%)	5 (6.2%)	0	3 (3.8%)	12 (4.3%)
15 to 28	2 (2.5%)	3 (3.8%)	0	1 (1.2%)	6 (2.1%)
29 to 42	1 (1.2%)	0	1 (2.5%)	1 (1.2%)	3 (1.1%)
43 to 56	2 (2.5%)	1 (1.2%)	0	0	3 (1.1%)
57 to 70	5 (6.2%)	1 (1.2%)	2 (5.0%)	0	8 (2.9%)
71 to 84	66 (82.5%)	70 (87.5%)	37 (92.5%)	74 (92.5%)	247 (88.2%)
> 84	0	0	0	1 (1.2%)	1 (0.4%)

* Includes unknowns.

Adverse Events

A total of 159 adverse events were reported on 116 patients during the study (Table 152.15). Analysis of the frequency of patients with reported adverse events demonstrated no significant differences between treatment groups ($P > 0.05$).

The Clindoxyl group had 36 (45.0%) patients that reported a total of 53 adverse events (Table 152.15). Eight of the 53 adverse events that were reported had a relationship to the study medication. These 8 adverse events were observed in 4 patients.

Treatment	# of patients	# of events ^b
Benzoyl Peroxide	36 (45.0%)	49
Clindamycin	28 (35.0%)	38
Vehicle	16 (40.0%)	19
Clindoxyl	36 (45.0%)	53
ALL	116 (41.4%)	159

* There was no significant difference between treatment groups when analyzed by Fisher's exact test, $p > 0.05$
^b Reoccurring events were counted once.

Additional Safety Observations

The tolerance of the study medication was determined by physician evaluation of erythema, peeling, and burning throughout the study and of overall tolerance at the last visit for each patient. All four treatments were well tolerated, except for occasional mild or rarely moderate erythema, peeling, burning, dryness, edema, or

pruritus. Local tolerance scores throughout the study were compared to baseline scores to compare the frequency of treatment emergent signs and symptoms in the four treatment groups (Table 152.16).

TABLE 152.16 Local Tolerance (Change from Baseline of Signs and Symptoms) in Study 152						
Signs and Symptoms	Treatment	Number of Patients with Worsening Score				
		Week 2	Week 5	Week 8	Week 11	Any ^a
Erythema	Benzoyl Peroxide	3(3.8%)	0	0	0	3 (3.8%)
	Clindamycin	1(1.3%)	0	0	1(1.4%)	2 (2.6%)
	Vehicle	0	0	0	0	0
	Clindoxyl	2(2.6%)	2(2.6%)	2(2.7%)	1(1.3%)	5 (6.4%)
Peeling	Benzoyl Peroxide	2(2.6%)	2(2.7%)	4(5.6%)	2(2.8%)	5 (6.3%)
	Clindamycin	1(1.3%)	1(1.4%)	2(2.8%)	1(1.4%)	3 (3.9%)
	Vehicle	0	0	0	0	0
	Clindoxyl	0	0	0	4(5.3%)	4 (5.1%)
Burning	Benzoyl Peroxide	3(3.8%)	2(2.7%)	1(1.4%)	1(1.4%)	5 (6.3%)
	Clindamycin	2(2.6%)	0	0	0	2 (2.6%)
	Vehicle	0	0	0	0	0
	Clindoxyl	1(1.3%)	0	0	1(1.3%)	2 (2.6%)
Dryness	Benzoyl Peroxide	2 (2.6%)	1 (1.4%)	3 (4.2%)	3 (4.2%)	4 (5.1%)
	Clindamycin	4 (5.3%)	2 (2.7%)	1 (1.4%)	1 (1.4%)	5 (6.5%)
	Vehicle	0	0	0	0	0
	Clindoxyl	3 (3.9%)	1 (1.3%)	0	0	3 (3.8%)

^a There were no significant differences ($p > 0.05$) between treatment groups of any worsening when analyzed by Fisher's exact test

There were no significant differences between the four treatment groups for change from baseline of signs and symptoms ($P > 0.05$). Most treatment emergent signs and symptoms were modest and involved a single grade worsening (i.e. absent to mild or mild to moderate).

Analysis of the distribution of patients by overall tolerance score, the primary safety variable, demonstrated no significant differences ($P > 0.05$) between the four treatment groups (Table 152.17). At least 94% of the patients in each group had excellent tolerance. There were 1 to 3 patients in each active treatment group that had poor to fair tolerance. All patients in the Vehicle group had excellent tolerance.

Treatment	Poor (0)	Fair (1)	Good (2)	Excellent (3)
Benzoyl Peroxide	1 (1.3%)	1 (1.3%)	1 (1.3%)	76 (96.2%)
Clindamycin	1 (1.3%)	2 (2.6%)	0	74 (96.1%)
Vehicle	0	0	0	40 (100.0%)
Clindoxyl	0	1 (1.3%)	4 (5.1%)	73 (93.6%)

* There was no significant difference between treatment groups ($p > 0.05$) when analyzed by Fisher's exact test

CONCLUSIONS ON SAFETY IN Study 152

Overall Study 152 demonstrates that once daily use of Clindoxyl is a safe regimen for the treatment of acne vulgaris. There were no significant difference between treatment groups relative to safety parameters. In the Clindoxyl group, overall tolerance was excellent in 94% of patients, treatment emergent signs and symptoms were modest in intensity, and only four (5%) patients had adverse events that were related to Clindoxyl treatment.

INTEGRATED SAFETY SUMMARY OF STUDIES 150, 151, AND 152

Table A presents number of patients reporting adverse events in Studies 150, 151, and 152 combined together. As can be seen from Table A, there was no significant difference ($P = 0.4$) between treatment groups in the incidence of patients reporting adverse events.

	Clindoxyl	Clindamycin	Benzoyl	Vehicle	All
# of patients	78 (41.5%)	67 (35.6%)	74 (39.4%)	36 (33.0%)	255 (37.9%)
Total # of patients	188	188	188	109	673

* There was no significant difference between treatment groups ($p = 0.4$, Chi-square test).

Summary and Conclusions (which may be conveyed to the sponsor)

A. EFFICACY

1. Study 150. *Study 150 supports the sponsor's claim that once daily use of Clindoxyl is an effective regimen for the treatment of acne vulgaris. Clindoxyl treatment was significantly ($P \leq 0.01$) more effective than Vehicle or Clindamycin treatments relative to the percent reduction of inflammatory or non-inflammatory lesions and in global improvement. Clindoxyl also was significantly ($P \leq 0.037$) better*

than Benzoyl with the exception of the percent reduction of non-inflammatory lesions ($P=0.3$). The ITT-LOCF analysis supported the results of the preferred analysis.

2. Study 151. Study 151 supports the sponsor's claim that once daily use of Clindoxyl is an effective regimen for the treatment of acne vulgaris. A significantly greater proportion of patients in the Clindoxyl group had good to excellent global improvement after 11 weeks than in the Vehicle, Benzoyl, or Clindamycin groups ($P\leq 0.013$). Clindoxyl treatment for 11 weeks produced significantly greater percent reductions in inflammatory lesions than Vehicle, Benzoyl and Clindamycin ($P<0.003$) and significantly greater percent reductions in non-inflammatory lesions than Clindamycin and Vehicle ($P\leq 0.003$). Greater lesion count reductions and greater global improvements in the Clindoxyl group were observed at earlier visits throughout the study. The ITT-LOCF analysis supported the results of the preferred analysis.

3. Study 152. Efficacy results were different at sites 152A and 152B. At site 152A, Clindoxyl produced a significantly greater ($P<0.019$) percent reduction at Week 11 of inflammatory and non-inflammatory lesion counts than Clindamycin or Vehicle. Compared to Benzoyl, Clindoxyl produced numerically (but not significantly) greater reduction of non-inflammatory and inflammatory lesions ($P\leq 0.5$). At site 152A, Clindoxyl had a numerically (but not significantly) greater proportion of patients with good to excellent global improvement at Week 11 than Clindamycin or Vehicle.

At site 152B, both Clindoxyl and Benzoyl produced very poor results compared with Clindamycin and Vehicle. Since Benzoyl performed unusually poorly at site 152B, the study at site 152B was considered a failed trial and ignored in the analysis.

4. COMBINED SITES 150 AND 152A. As Study 150 had only one center, data from Study 150 and Site 152A were combined. Analysis of the combined data supports the sponsor's claim that once daily use of Clindoxyl is effective for treatment acne vulgaris. Clindoxyl treatment was significantly ($P\leq 0.001$) more effective than Vehicle or Clindamycin treatments relative to the percent reduction of inflammatory or non-inflammatory lesions and in global improvement. Clindoxyl also was significantly ($P\leq 0.037$) better than Benzoyl with the exception of the percent reduction of non-inflammatory lesions ($P=0.1$).

B. SAFETY.

Safety analyses in studies 150, 151, and 152 showed that there were no significant differences ($P>0.05$) between treatment groups relative to overall tolerance scores. In the Clindoxyl group, overall tolerance was excellent in more than 92% of patients. There were also no significant differences ($P>0.05$) between treatment groups relative to the treatment emergent signs and symptoms. Most treatment emergent signs and symptoms involved a modest (1 grade) worsening. There were no significant differences ($P>0.05$) between treatments in the incidence of patients with adverse events. Integrated safety analysis supported safety results for individual studies.

OVERALL CONCLUSIONS (which may be conveyed to the sponsor)

Overall, Studies 150, 151, and 152A support the sponsor's claim that once daily use of Clindoxyl is a safe and effective regimen for the treatment of acne vulgaris.

Studies 150 and 152A are single center studies and the combined analysis of these two studies also strongly support the sponsor's claim that once daily use of Clindoxyl is a safe and effective regimen for the treatment of acne vulgaris.

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This review contains 49 pages including 43 tables and 10 figures.
WordPerfect 6.1/NDA50741/clindoxy.re1/01-22-97

STATISTICAL/CLINICAL REVIEW AND EVALUATION

(ADDENDUM)

MAY 12 1997

NDA#/Drug class: 50-741/4S

Applicant: Stiefel laboratories, Inc.
Coral Gables, Fl 33134

Name of Drug: Clindoxyl Gel (5% benzoyl peroxide and clindamycin phosphate equivalent to 1% clindamycin, packaging Lot #292313)

Documents Reviewed: Volumes 1.17-1.26 dated May 14, 1996, and data on disks provided by the sponsor

Type of Report: Statistical/Clinical.

Indication: Topical treatment of facial acne vulgaris

Clinical Input: Susan Walker, M.D. (HFD-540)

INTRODUCTION

Three controlled clinical studies (Protocols 150, 151, and 152) were conducted with clindoxyl gel to determine safety and efficacy in the topical treatment of acne vulgaris. Clindoxyl gel is a combination product containing 5% benzoyl peroxide and clindamycin phosphate equivalent to 1% clindamycin. The clinical trials included 3 control groups, 5% benzoyl peroxide gel, clindamycin phosphate gel (equivalent to 1% clindamycin) and vehicle gel, with the purpose to compare the efficacy and safety of clindoxyl gel in the treatment of acne vulgaris with that of vehicle or either of the individual active components of the product.

Throughout the addendum, the terms 'Study 150', 'Study 151' and "Study 152' refer to the three clinical trials submitted by the sponsor, and the treatment name abbreviations Clindoxyl, Benzoyl, and Clindamycin refer to combination product containing 5% benzoyl peroxide and clindamycin phosphate equivalent to 1% clindamycin, benzoyl peroxide gel, and clindamycin phosphate gel (equivalent to 1% clindamycin), respectively. Term 'significant' means statistically significant at the 0.05 level.

Study 151 had four sites. Study 152 had two sites: 152A and 152B. Study 150 had only one site and, therefore, will be considered as supportive to the pivotal studies 151 and 152. At site 152B, both Clindoxyl and Benzoyl produced very poor results compared with Vehicle and Clindamycin. Since Benzoyl performed unusually poorly

at site 152B, it was originally decided to consider Study 152 a failed trial and ignore it in efficacy analysis.

However, later the Division decided not to exclude the site 152B. This Addendum is intended to analyze results of all sites in NDA 50-741 and provide amended efficacy conclusions.

Clindoxyl is a combination drug indicated to cure two types of lesions: inflammatory and non-inflammatory. One of two components, Benzoyl, is known to cure non-inflammatory lesions and the other component, Clindamycin, is known to cure inflammatory lesions.

According to regulatory requirements, the sponsor must demonstrate that both components contribute to efficacy of Clindoxyl in treatment of acne vulgaris. Therefore, Clindoxyl must be statistically significantly better than Vehicle relative to reduction from baseline in inflammatory and non-inflammatory lesion counts. Clindoxyl also must be no worse than Benzoyl and significantly better than Clindamycin relative to reduction of non-inflammatory lesion count from baseline. Clindoxyl also must be no worse than Clindamycin and significantly better than Benzoyl relative to reduction of inflammatory lesion count from baseline.

In addition, Benzoyl must be statistically significantly better than Vehicle relative to reduction of non-inflammatory lesion count from baseline and Clindamycin must be statistically significantly better than Vehicle relative to reduction of inflammatory lesion count from baseline.

RESULTS

NON-INFLAMMATORY LESIONS

Relative to non-inflammatory lesions, contribution of Benzoyl to efficacy of Clindoxyl must be demonstrated. Relative to non-inflammatory lesions, Clindoxyl must be no worse than Benzoyl and Clindoxyl must be statistically significantly better than Vehicle and Clindamycin.

Tables 1-4 present actual reduction from baseline and percent reduction from baseline in non-inflammatory lesion counts in Studies 150, 151, and 152. Clindoxyl was significantly better than Vehicle relative to actual reduction ($p \leq 0.04$) and percent reduction ($p \leq 0.037$). Clindoxyl was significantly better than Clindamycin relative to actual reduction ($p < 0.012$) in pivotal Studies 151 and 152. Clindoxyl also was significantly better than Clindamycin relative to percent reduction ($p < 0.007$) in all three Studies 150, 151, and 152. Clindoxyl was no worse than Benzoyl relative to both actual reduction and percent reduction in non-inflammatory lesions in Studies 151 and 152 ($0.079 \leq p \leq 0.456$). Benzoyl was significantly better than Vehicle relative to actual and percent reduction of non-inflammatory lesion count in Studies 150 and 151 ($p < 0.03$). However, in Study 152, Benzoyl was not significantly better than Vehicle

relative to both actual and percent reduction of non-inflammatory lesion count ($p \geq 0.234$).

Treatment Comparison		Statistic ^b	Least Square Mean			p-Value
First	Second		First	Second	Difference	
Clindoxyl	Vehicle	Reduction at Week 11	12.0	-4.3	16.3	0.040
		% Reduction at Week 11	26.5	-12.6	39.1	0.001
Clindoxyl	Benzoyl	Reduction at Week 11	12.0	14.7	-2.7	0.738
		% Reduction at Week 11	26.5	14.2	12.3	0.309
Clindoxyl	Clindamycin	Reduction at Week 11	12.0	-0.6	12.6	0.105
		% Reduction at Week 11	26.5	-5.2	31.7	0.007
Benzoyl Peroxide	Vehicle	Reduction at Week 11	14.7	-4.3	19.0	0.021
		% Reduction at Week 11	14.2	-12.6	26.8	0.030
Clindamycin	Vehicle	Reduction at Week 11	-0.6	-4.3	3.7	0.633
		% Reduction at Week 11	-5.2	-12.6	7.3	0.527

^b Reduction (actual reduction) = baseline count - count at a later week

Treatment Comparison		Statistic ^b	Least Square Mean			p-Value
First	Second		First	Second	Difference	
Clindoxyl	Vehicle	Reduction at Week 11	18.3	1.1	17.2	0.001
		% Reduction at Week 11	40.1	-10.5	50.6	0.000
Clindoxyl	Benzoyl Peroxide	Reduction at Week 11	18.3	16.0	2.3	0.549
		% Reduction at Week 11	40.1	34.0	6.1	0.456
Clindoxyl	Clindamycin	Reduction at Week 11	18.3	8.1	10.2	0.012
		% Reduction at Week 11	40.1	14.5	25.6	0.003
Benzoyl Peroxide	Vehicle	Reduction at Week 11	16.0	1.1	14.9	0.003
		% Reduction at Week 11	34.0	-10.5	44.5	0.000
Clindamycin	Vehicle	Reduction at Week 11	8.1	1.1	7.0	0.166
		% Reduction at Week 11	14.5	-10.5	25.0	0.018

^b Reduction (actual reduction) = baseline count - count at a later week.

TABLE 3
Actual Reduction at Week 11 of Non-Inflammatory Lesion Counts in Study 152
Results of Statistical Analyses in the Preferred Data Set

Treatment Comparison			Least Square Mean			
First	Second	Site	First	Second	Difference	p-Value
Clindoxyl	Vehicle	152A	23.0	7.8	15.2	0.005
		152B	2.2	3.2	-0.9	0.205
		ALL	12.6	5.5	7.1	0.008
Clindoxyl	Benzoyl Peroxide	152A	23.0	16.2	6.8	0.128
		152B	2.2	1.2	1.0	0.082
		ALL	12.6	8.7	3.9	0.079
Clindoxyl	Clindamycin	152A	23.0	6.2	16.8	0.000
		152B	2.2	2.9	-0.7	0.256
		ALL	12.6	4.5	8.1	0.000
Benzoyl Peroxide	Vehicle	152A	16.2	7.8	8.4	0.117
		152B	1.2	3.2	-2.0	0.008
		ALL	8.7	5.5	3.2	0.234
Clindamycin	Vehicle	152A	6.2	7.8	-1.6	0.764
		152B	2.9	3.2	-0.3	0.732
		ALL	4.5	5.5	-0.9	0.731

Actual reduction = baseline count - count at a later week.

TABLE 4
Percent Reduction at Week 11 of Non-Inflammatory Lesion Counts in Study 152
Results of Statistical Analyses in the Preferred Data Set

Treatment Comparison			Least Square Mean			
First	Second	Site	First	Second	Difference	p-Value
Clindoxyl	Vehicle	152A	41.8	17.4	24.4	0.010
		152B	10.0	13.3	-3.3	0.371
		ALL	25.9	15.3	10.5	0.037
Clindoxyl	Benzoyl Peroxide	152A	41.8	31.5	10.3	0.191
		152B	10.0	6.2	3.8	0.202
		ALL	25.9	18.8	7.0	0.091
Clindoxyl	Clindamycin	152A	41.8	9.0	32.8	0.000
		152B	10.0	13.3	-3.3	0.271
		ALL	25.9	11.1	14.7	0.000
Benzoyl Peroxide	Vehicle	152A	31.5	17.4	14.1	0.135
		152B	6.2	13.3	-7.1	0.056
		ALL	18.8	15.3	3.5	0.490
Clindamycin	Vehicle	152A	9.0	17.4	-8.4	0.373
		152B	13.3	13.3	0.0	0.998
		ALL	11.1	15.3	-4.2	0.406

INFLAMMATORY LESIONS.

Relative to inflammatory lesions, contribution of Clindamycin to efficacy of Clindoxyl must be demonstrated. Relative to inflammatory lesions, Clindoxyl must be no worse than Clindamycin and Clindoxyl must be statistically significantly better than Vehicle and Benzoyl.

Tables 5-8 provide actual reduction from baseline and percent reduction from baseline in inflammatory lesion counts in Studies 150, 151, and 152. Clindoxyl was significantly better than Vehicle relative to actual reduction ($p \leq 0.046$) in all three studies. Relative to percent reduction in inflammatory lesions, Clindoxyl was significantly better than Vehicle ($p \leq 0.0001$) in Studies 150 and 151. In Study 152, Clindoxyl was marginally significantly better than Vehicle relative to percent reduction of inflammatory lesion count ($p = 0.051$).

In the pivotal Study 152, Clindoxyl was not significantly better than Benzoyl relative to either actual or percent reduction in inflammatory lesions ($p \geq 0.107$). In the other pivotal Study 151, the difference between the Clindoxyl and Benzoyl groups in the mean lesion count reduction was only 2.3 ($p = 0.278$, Table 6). Relative to the percent reduction, this corresponds to the difference of 19.3% between the two treatment groups ($p = 0.003$).

In the supportive Study 150, the difference between the Clindoxyl and Benzoyl groups in the mean lesion count reduction was only 2.9 ($p = 0.508$, Table 5). Relative to the percent reduction, this corresponds to the difference of 27.0% between the two treatment groups ($p = 0.037$).

Clindamycin was significantly better than Vehicle relative to inflammatory lesions only in Study 151 ($p \leq 0.001$). In Studies 150 and 152, Clindamycin was not significantly better than Vehicle ($p \geq 0.139$, Table 5, 7, and 8) relative to either actual or percent reduction of inflammatory lesion count.

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Treatment Comparison		Statistic ^b	Least Square Mean			p-Value
First	Second		First	Second	Difference	
Clindoxyl	Vehicle	Reduction at Week 11	17.0	8.1	8.9	0.040
		% Reduction at Week 11	66.5	19.2	47.3	0.000
Clindoxyl	Benzoyl	Reduction at Week 11	17.0	14.1	2.9	0.508
		% Reduction at Week 11	66.5	39.5	27.0	0.037
Clindoxyl	Clindamycin	Reduction at Week 11	17.0	13.0	4.0	0.345
		% Reduction at Week 11	66.5	34.5	32.0	0.010
Benzoyl	Vehicle	Reduction at Week 11	14.1	8.1	5.9	0.183
		% Reduction at Week 11	39.5	19.2	20.2	0.120
Clindamycin	Vehicle	Reduction at Week 11	13.0	8.1	4.9	0.250
		% Reduction at Week 11	34.5	19.2	15.3	0.218

^b Reduction (actual reduction) = baseline count - count at a later week

Treatment Comparison		Statistic ^b	Least Square Mean			p-Value
First	Second		First	Second	Difference	
Clindoxyl	Vehicle	Reduction at Week 11	14.5	-1.3	15.9	0.000
		% Reduction at Week 11	58.0	-10.7	68.6	0.000
Clindoxyl	Benzoyl Peroxide	Reduction at Week 11	14.5	12.2	2.3	0.278
		% Reduction at Week 11	58.0	38.7	19.3	0.003
Clindoxyl	Clindamycin	Reduction at Week 11	14.5	8.1	6.4	0.005
		% Reduction at Week 11	58.0	34.6	23.4	0.000
Benzoyl Peroxide	Vehicle	Reduction at Week 11	12.2	-1.3	13.5	0.000
		% Reduction at Week 11	38.7	-10.7	49.4	0.000
Clindamycin	Vehicle	Reduction at Week 11	8.1	-1.3	9.5	0.001
		% Reduction at Week 11	34.6	-10.7	45.2	0.000

^b Reduction (actual reduction) = baseline count - count at a later week

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Treatment Comparison			Least Square Mean			
First	Second	Site	First	Second	Difference	p-Value
Clindoxyl	Vehicle	152A	11.5	4.4	7.1	0.010
		152B	6.1	7.2	-1.0	0.444
		ALL	8.8	5.8	3.0	0.046
Clindoxyl	Benzoyl Peroxide	152A	11.5	10.3	1.2	0.597
		152B	6.1	3.7	2.4	0.032
		ALL	8.8	7.0	1.8	0.151
Clindoxyl	Clindamycin	152A	11.5	6.9	4.6	0.043
		152B	6.1	9.2	-3.1	0.006
		ALL	8.8	8.0	0.8	0.538
Benzoyl Peroxide	Vehicle	152A	10.3	4.4	5.9	0.031
		152B	3.7	7.2	-3.4	0.013
		ALL	7.0	5.8	1.2	0.420
Clindamycin	Vehicle	152A	6.9	4.4	2.4	0.370
		152B	9.2	7.2	2.1	0.131
		ALL	8.0	5.8	2.2	0.139

Actual reduction = baseline count - count at a later week.

Treatment Comparison			Least Square Mean			
First	Second	Site	First	Second	Difference	p-Value
Clindoxyl	Vehicle	152A	54.4	18.5	35.9	0.007
		152B	32.7	39.2	-6.6	0.360
		ALL	43.5	28.9	14.7	0.051
Clindoxyl	Benzoyl Peroxide	152A	54.4	46.1	8.3	0.448
		152B	32.7	21.0	11.7	0.048
		ALL	43.5	33.5	10.0	0.107
Clindoxyl	Clindamycin	152A	54.4	28.2	26.2	0.019
		152B	32.7	50.8	-18.2	0.002
		ALL	43.5	39.5	4.0	0.517
Benzoyl Peroxide	Vehicle	152A	46.1	18.5	27.6	0.038
		152B	21.0	39.2	-18.3	0.013
		ALL	33.5	28.9	4.7	0.537
Clindamycin	Vehicle	152A	28.2	18.5	9.7	0.464
		152B	50.8	39.2	11.6	0.109
		ALL	39.5	28.9	10.7	0.158

SUMMARY AND CONCLUSIONS (which may be conveyed to the sponsor)

Studies 151 and 152 will be considered pivotal studies. Study 150 had only one site and, therefore, will be considered as supportive to the pivotal studies 151 and 152.

According to regulatory requirements, the sponsor must demonstrate that both components contribute to efficacy of Clindoxyl in treatment of acne vulgaris. Clindoxyl must be statistically significantly better than Vehicle relative to reduction from baseline in inflammatory and non-inflammatory lesion counts. Clindoxyl also must be no worse than Benzoyl and significantly better than Clindamycin relative to reduction of non-inflammatory lesion count from baseline. Clindoxyl also must be no worse than Clindamycin and significantly better than Benzoyl relative to reduction of inflammatory lesion count from baseline.

In addition, Benzoyl must be statistically significantly better than Vehicle relative to reduction of non-inflammatory lesion count from baseline and Clindamycin must be statistically significantly better than Vehicle relative to reduction of inflammatory lesion count from baseline.

The results of pivotal Studies 151 and 152 **demonstrate that Benzoyl contributes to efficacy of Clindoxyl in treatment of non-inflammatory lesions.** Relative to non-inflammatory lesions, Clindoxyl was statistically significantly better than Vehicle and Clindamycin ($p < 0.04$, Tables 2-4) and no worse than Benzoyl ($0.079 \leq p \leq 0.456$, Tables 2-4). The results of Study 150 support the pivotal Studies 151 and 152.

However, the **results of Studies 150, 151, and 152 do not provide statistical evidence that Clindamycin contributes to efficacy of Clindoxyl in treatment of inflammatory lesions.**

In the pivotal Study 152, **Clindoxyl was not significantly better than Benzoyl relative to either actual or percent reduction of inflammatory lesion count** ($p \geq 0.107$, Tables 7 and 8).

In the other pivotal Study 151, the difference between the Clindoxyl and Benzoyl groups in the mean lesion count reduction was only 2.3 ($p = 0.278$, Table 6). Relative to the percent reduction of inflammatory lesion count, this corresponds to the difference of 19.3% between the two treatment groups ($p = 0.003$). As the actual difference between the treatment groups is very small (2.3 lesions), not statistically significant ($p = 0.278$), and probably not clinically meaningful, the results of pivotal Study 151 cannot be considered to be supporting the claim that Clindamycin contributes to the efficacy of Clindoxyl in treatment of inflammatory lesions.

In the supportive Study 150, the difference between the Clindoxyl and Benzoyl groups in the mean lesion count reduction was only 2.9 ($p = 0.508$, Table 5). Relative to the percent reduction of inflammatory lesion count, this corresponds to the difference of 27.0% between the two treatment groups ($p = 0.037$). As the actual difference between the treatment groups is very small (2.9 lesions) and not statistically

significant ($p = 0.508$), the results of Study 150 cannot be considered to be supporting the claim that Clindamycin contributes to the efficacy of Clindoxyl in treatment of inflammatory lesions.

In addition, in Studies 150 and 152, Clindamycin was not significantly better than Vehicle ($p \geq 0.139$, Tables 5, 7, and 8) relative to either actual or percent reduction of inflammatory lesion count.

OVERALL CONCLUSIONS:

The results of Studies 150, 151 and 152 demonstrate that Benzoyl contributes to the efficacy of Clindoxyl in treatment of non-inflammatory lesions. However, the results of Studies 150, 151, and 152 do not provide statistical evidence that Clindamycin contributes to the efficacy of Clindoxyl in treatment of inflammatory lesions. Therefore, overall, the sponsor failed to provide enough statistical evidence that the combination drug Clindoxyl is efficacious in treatment of acne vulgaris.

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Archival NDA 50-741

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This Addendum contains 9 pages including 8 tables.

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STATISTICAL REVIEW AND EVALUATION

Medical Division: **Division of Dermatologic & Dental Drug Products (DDDDP)**
HFD-540
Biometrics Division: **Division of Biometrics III**
HFD-725

NDA NUMBER: 50-741
SERIAL NUMBER: 000/AZ
DATE RECEIVED BY CENTER: 2/26/2002
DRUG NAME: Clindoxyl Topical Gel
(clindamycin/benzoyl peroxide)
INDICATION: Acne (Inflammatory Lesions)
SPONSOR: Stiefel
DOCUMENTS REVIEWED: Vol. 36.4 (submitted 2/26/02), Vol. 1.18,
1.20, & 1.23 (submitted 5/03/96), and
Vol. 15.21 & 15.26 (submitted 3/06/00)
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1 Executive Summary of Statistical Findings

1.1 Conclusions and Recommendations

Clindoxyl is a combination product containing benzoyl peroxide and clindamycin. The sponsor has demonstrated the superiority of Clindoxyl versus benzoyl peroxide, clindamycin, and vehicle for the percent reduction in inflammatory lesions and global improvement in three out of five clinical studies (Studies 150, 151, and 158). Study 152 did not demonstrate statistical significance between Clindoxyl and benzoyl peroxide, clindamycin, or vehicle for either percent reduction in inflammatory lesions or global improvement. Study 156 demonstrated the statistical superiority of Clindoxyl to clindamycin but not benzoyl peroxide in terms of percent reduction in inflammatory lesions. Also for Study 156, the comparisons between Clindoxyl and benzoyl peroxide and clindamycin were not significant in terms of global improvement. With three positive studies, the sponsor has submitted sufficient information to statistically support a limited indication for the treatment of inflammatory lesions.

1.2 Overview of Clinical Program and Studies Reviewed

The sponsor originally submitted three studies to support the efficacy of Clindoxyl for the treatment of moderate to moderately severe acne (Studies 150, 151, and 152). When these studies failed to demonstrate that Clindoxyl was superior to benzoyl peroxide for non-inflammatory lesions, the sponsor conducted two additional studies (Studies 156 and 158). These studies also failed to demonstrate the superiority of Clindoxyl to benzoyl peroxide for non-inflammatory lesions. Subsequently, the sponsor has amended the application to request that Clindoxyl be considered for the more limited indication of inflammatory lesions. To this end, the five submitted studies are reviewed to assess the efficacy of Clindoxyl in terms of percent reduction in inflammatory lesions and global improvement. For more detailed reviews of these five studies, including subgroup and safety assessments, refer to the original statistical reviews dated 2/10/1997, 5/09/1997, and 7/17/2000.

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2 Statistical Review and Evaluation of Evidence

2.1 Introduction and Background

The application for Clindoxyl (NDA 50-741) for the treatment of acne was originally submitted in May 1996. Clindoxyl is a combination product containing clindamycin and benzoyl peroxide. The original application included 3 clinical studies: 150, 151 and 152. Each study evaluated four arms: Clindoxyl (clindamycin/benzoyl peroxide), clindamycin, benzoyl peroxide, and vehicle. The primary endpoints in each study were the percent reduction in inflammatory and non-inflammatory lesions. In addition, the proportion of subjects with good to excellent global improvement were analyzed. The analyses were based on the per protocol population (called the "preferred" population). The reviewers concluded that the efficacy contribution of the benzoyl peroxide to the complete product was established, but the efficacy contribution of the clindamycin was inconclusive. Thus, the product was not approved, and in May 1997 the Agency recommended that the sponsor conduct an additional study to establish the efficacy contribution of clindamycin to the combination product.

In March 2000, the sponsor submitted two new studies: 156 and 158. For the two studies, the primary analyses were the percent reduction in non-inflammatory, inflammatory, and total lesions. In addition the proportion of subjects with good to excellent global improvement were analyzed. The analysis population was ITT/LOCF. Study 158 was a 4-arm study like the previous studies, but Study 156 did not have a vehicle arm. Studies 156 and 158 also failed to adequately demonstrate that clindamycin contributes to the efficacy of Clindoxyl. In September 2000, the Agency sent another NA letter for this application.

The sponsor responded by noting that Study 150 (a single-center study with 30 patients per treatment arm) met the Division's criteria for efficacy (statistical significance for 2 out of 3 types of lesions, plus significance on the investigator's global) if the ITT/LOCF analysis population was considered, rather than the "preferred" population that was submitted in the original submission. The sponsor also noted that their studies demonstrated results if only inflammatory lesions and the global assessment were considered, and requested a limited indication for inflammatory lesions only. The sponsor has submitted a re-analysis of Study 150 using the ITT/LOCF population rather than the preferred population, along with a similar analysis for the global investigator assessment score. The sponsor also submitted proposed labeling for the indication of inflammatory acne lesions only. This review focuses on whether the ITT analyses of the sponsor's studies can support the more limited claim for the treatment of inflammatory lesions only.

2.2 Data Analyzed and Sources

The clinical program for Clindoxyl consisted of 5 studies, all conducted in the United States. Table 1 displays the number of subjects enrolled in clinical trials for Clindoxyl. For complete reviews of these studies refer to the statistical reviews dated 2/10/1997 and

5/09/1997 for Studies 150, 151, and 152, and dated 7/17/2000 for Studies 156 and 158. This review focuses on the analyses relating to the percent reduction in inflammatory lesions in each study.

Table 1 – Subjects Enrolled in the Clinical Program for Clindoxyl

	<i>Study Number</i>				
	150	151	152	156	158
Clindoxyl	30	78	80	96	113
Benzoyl Per.	30	78	80	96	112
Clindamycin	30	78	80	96	65
Vehicle	30	39	40	--	68
Total	120	273	280	288	358

2.3 Statistical Evaluation of Evidence on Efficacy

2.3.1 Statistical Methodology

In each study (150, 151, 152, 156, and 158), subjects were evaluated for the number of inflammatory and non-inflammatory lesions at baseline and Weeks 2, 5, 8, and 11. The primary efficacy timepoint is Week 11. In addition to the lesion counts, subjects were graded by the physician on the global assessment of improvement relative to baseline on the scale: 0 = worsening, 1 = 0-25% improvement (poor), 2 = 26-50% improvement (fair), 3 = 51-75% improvement (good), and 4 = 76-100% improvement (excellent). For lesion counts, the primary endpoint was percent reduction from baseline to Week 11. The percent reduction in lesion counts was analyzed with ANOVA with factors of treatment, center, and treatment by center interaction. In the multi-center studies (all studies except 150), the sponsor used least squares means (adjusted for site) to estimate the percent reduction. In this review ordinary means rather than least squares means are presented. Global improvement was dichotomized to success/failure by counting subjects with 'good' to 'excellent' improvement as successes. The success rate was analyzed with logistic regression with factors for treatment and center. In this amendment, all analyses are for the ITT population (all randomized subjects) with LOCF for missing data.

2.3.2 Inflammatory Lesions Indication

Previous reviews of the sponsor's studies concluded that there was insufficient evidence to support the full indication of acne, primarily because Clindoxyl failed to consistently demonstrate superiority to benzoyl peroxide for non-inflammatory lesions. However, the pattern of efficacy for inflammatory lesions was more promising. To establish the efficacy of Clindoxyl for inflammatory lesions, this review will assess the efficacy of Clindoxyl versus its components (benzoyl peroxide, clindamycin, and vehicle) in terms of percent reduction in inflammatory lesions. The physician's global improvement assessment will also be considered.

2.3.3 Efficacy Results for Inflammatory Lesions and Global Improvement

2.3.3.1 Study 150

Study 150 enrolled 120 subjects, 30 on each arm (Clindoxyl, benzoyl peroxide, clindamycin, vehicle). Study 150 is a single-center study. Of the 120 enrolled subjects, 108 subjects completed the study. The efficacy results for inflammatory lesions by treatment arm are summarized in Table 2.

Table 2 – Mean number of Baseline and Week 11 Inflammatory Lesions and Mean Percent Reduction in Inflammatory Lesions from Baseline to Week 11 in Study 150 (ITT/LOCF)

Inflammatory Lesions - Study 150				
	<i>N</i>	<i>Baseline</i>	<i>Week 11</i>	<i>Percent Reduction</i>
Clindoxyl	30	26.5	10.1	64.8%
Benzoyl Per.	30	34.0	20.6	36.4%
Clindamycin	30	30.5	17.8	33.9%
Vehicle	30	34.7	26.5	19.4%

Source: Sponsor's submission, Vol. 1.18, pg. 98 (5/03/96).

To establish the efficacy of Clindoxyl for inflammatory lesions, Clindoxyl should be superior to each of the remaining arms: benzoyl peroxide, clindamycin, and vehicle. The p-values for these comparisons are presented in Table 3. The p-values are based on an ANOVA model with the effect of treatment. All three comparisons are significant at the 0.05 level for Study 150. The p-values for global improvement comparing the percentage of subjects with 'good' to 'excellent' improvement on the different treatments are also presented in Table 3. All three comparisons with Clindoxyl for global improvement are significant at the 0.05 level for Study 150. Thus, Study 150 supports the efficacy of Clindoxyl for the treatment of inflammatory lesions.

Table 3 – Treatment Effect P-values for Percent Reduction in Inflammatory Lesions from Baseline to Week 11 and Success in Global Improvement in Study 150 (ITT/LOCF)

Study 150	<i>Inflammatory Lesions p-value</i>	<i>Global Improvement p-value</i>
Clindoxyl vs. Vehicle	0.0002	0.0001
Clindoxyl vs. Benzoyl Per.	0.0169	0.0217
Clindoxyl vs. Clindamycin	0.0095	0.0112

Source: Sponsor's Submission, Vol. 36.4, pg. 3 (2/26/02).

2.3.3.2 Study 151

Study 151 enrolled 273 subjects, 78 subjects on the Clindoxyl, benzoyl peroxide, and clindamycin arms, and 39 subjects on the vehicle arm. Study 151 had 4 centers. Centers

A, B, and C each enrolled 70 subjects, and Center D enrolled 63 subjects. Of the 273 enrolled subjects, 231 completed the study. The efficacy results for inflammatory lesions by treatment arm are summarized in Table 4.

Table 4 – Mean number of Baseline and Week 11 Inflammatory Lesions and Mean Percent Reduction in Inflammatory Lesions from Baseline to Week 11 in Study 151 (ITT/LOCF)

Inflammatory Lesions – Study 151				
	<i>N</i>	<i>Baseline</i>	<i>Week 11</i>	<i>Percent Reduction</i>
Clindoxyl	78	26.4	12.4	55.6%
Benzoyl Per.	78	29.2	17.7	37.1%
Clindamycin	78	25.5	18.5	29.6%
Vehicle	39	27.6	26.5	-0.4%

Source: Sponsor's submission Vol. 1.20, pg. 140 (5/03/96).

Table 5 presents the p-values for comparing Clindoxyl to benzoyl peroxide, clindamycin, and vehicle. The p-values are based on an ANOVA model with the effects of treatment, center, and treatment by center interaction. All three comparisons with Clindoxyl are significant at the 0.05 level for Study 151. The p-values for global improvement comparing the percentage of subjects with 'good' to 'excellent' improvement on each treatment are also presented in Table 5. All three comparisons for global improvement are significant at the 0.05 level for Study 151. Thus, Study 151 supports the efficacy of Clindoxyl for the treatment of inflammatory lesions.

Table 5 – Treatment Effect P-values for Percent Reduction in Inflammatory Lesions from Baseline to Week 11 and Success in Global Improvement in Study 151 (ITT/LOCF)

Study 151	<i>Inflammatory Lesions p-value</i>	<i>Global Improvement p-value</i>
Clindoxyl vs. Vehicle	<0.0001	<0.0001
Clindoxyl vs. Benzoyl Per.	0.0019	0.0299
Clindoxyl vs. Clindamycin	<0.0001	0.0005

Source: Sponsor's Submission, Vol. 36.4, pg. 4 (2/26/02).

2.3.3.3 Study 152

Study 152 enrolled 280 patients, 80 subjects on the Clindoxyl, benzoyl peroxide, and clindamycin arms, and 40 subjects on the vehicle arm. Study 152 had 2 centers, each with 140 subjects. Of the 280 enrolled subjects, 255 completed the study. The efficacy results for inflammatory lesions by treatment arm are summarized in Table 6.

Table 6 – Mean number of Baseline and Week 11 Inflammatory Lesions and Mean Percent Reduction in Inflammatory Lesions from Baseline to Week 11 in Study 152 (ITT/LOCF)

Inflammatory Lesions – Study 152				
	<i>N</i>	<i>Baseline</i>	<i>Week 11</i>	<i>Percent Reduction</i>
Clindoxyl	80	20.7	12.3	41.7%
Benzoyl Per.	80	21.3	14.6	31.6%
Clindamycin	80	20.0	12.5	37.5%
Vehicle	40	21.5	15.8	29.2%

Source: Sponsor's submission Vol. 1.23, pg. 133 (5/03/96).

Table 7 presents the p-values for comparing Clindoxyl to benzoyl peroxide, clindamycin, and vehicle. The p-values are based on an ANOVA model with the effects of treatment, center, and treatment by center interaction. None of the three comparisons are significant at the 0.05 level for Study 152, although the p-values for Clindoxyl versus vehicle and Clindoxyl versus benzoyl peroxide are both <0.10, and the data is trending in the direction favoring Clindoxyl for these two comparisons. The p-values for global improvement comparing the percentage of subjects with 'good' to 'excellent' improvement on each treatment are also presented in Table 7. Like the p-values for the percent reduction in inflammatory lesions, none of the three comparisons are significant at the 0.05 level for Study 152. Thus, Study 152 does not demonstrate statistical significance for either inflammatory lesions or global improvement, although there is some evidence of a trend for inflammatory lesions for the comparisons of Clindoxyl versus vehicle and benzoyl peroxide with p-values < 0.10.

Table 7 – Treatment Effect P-values for Percent Reduction in Inflammatory Lesions from Baseline to Week 11 and Success in Global Improvement in Study 152 (ITT/LOCF)

Study 152	<i>Inflammatory Lesions p-value</i>	<i>Global Improvement p-value</i>
Clindoxyl vs. Vehicle	0.0784	0.4852
Clindoxyl vs. Benzoyl Per.	0.0820	0.8622
Clindoxyl vs. Clindamycin	0.4743	0.1354

Source: Sponsor's Submission, Vol. 36.4, pg. 5 (2/26/02).

2.3.3.4 Study 156

Study 156 enrolled 288 patients, with 96 subjects on each arm (Clindoxyl, benzoyl peroxide, and clindamycin). Study 156 did not have a vehicle arm. This study had 8 centers, each with 36 subjects. Of the 288 enrolled subjects, 257 completed the study. The efficacy results for inflammatory lesions by treatment arm are summarized in Table 8.

Table 8 – Mean number of Baseline and Week 11 Inflammatory Lesions and Mean Percent Reduction in Inflammatory Lesions from Baseline to Week 11 in Study 156 (ITT/LOCF)

Inflammatory Lesions – Study 156				
	<i>N</i>	<i>Baseline</i>	<i>Week 11</i>	<i>Percent Reduction</i>
Clindoxyl	96	32.9	14.2	57.3%
Benzoyl Per.	96	33.6	15.0	56.7%
Clindamycin	96	34.5	18.2	48.6%

Source: Sponsor's Submission, Vol. 15.21, pg. 73 (3/06/00).

Table 9 presents the p-values for comparing Clindoxyl to benzoyl peroxide and clindamycin. The p-values are based on an ANOVA model with the effects of treatment, center, and treatment by center interaction. The Clindoxyl versus clindamycin comparison is significant at the 0.05 level ($p = 0.030$), but the Clindoxyl versus benzoyl peroxide comparison is not ($p = 0.845$). The p-values for global improvement comparing the percentage of subjects with 'good' to 'excellent' improvement are also presented in Table 9. Neither comparison for global improvement is significant at the 0.05 level for Study 156. Thus, Study 156 only demonstrates statistical significance for one of the two comparisons for inflammatory lesions and for neither comparison for global improvement.

Table 9 – Treatment Effect P-values for Percent Reduction in Inflammatory Lesions from Baseline to Week 11 and Success in Global Improvement in Study 156 (ITT/LOCF)

Study 156	<i>Inflammatory Lesions p-value</i>	<i>Global Improvement p-value</i>
Clindoxyl vs. Benzoyl Per.	0.845	0.213
Clindoxyl vs. Clindamycin	0.030	0.088

Source: Sponsor's Submission, Vol. 15.21, pg. 109 and 224 (3/06/00).

2.3.3.5 Study 158

Study 158 enrolled 358 patients, with 113 subjects on the Clindoxyl arm, 112 on the benzoyl peroxide arm, 65 on the clindamycin arm, and 68 on the vehicle arm. This study had 8 centers, each with between 30 and 50 subjects. Of the 358 enrolled subjects, 289 completed the study. The efficacy results for inflammatory lesions by treatment arm are summarized in Table 10.

Table 10 – Mean number of Baseline and Week 11 Inflammatory Lesions and Mean Percent Reduction in Inflammatory Lesions from Baseline to Week 11 in Study 158 (ITT/LOCF)

Inflammatory Lesions – Study 158				
	<i>N</i>	<i>Baseline</i>	<i>Week 11</i>	<i>Percent Reduction</i>
Clindoxyl	113	32.5	15.3	52.1%
Benzoyl Per.	112	31.3	18.5	41.0%
Clindamycin	65	33.1	22.9	32.6%
Vehicle	68	30.6	22.5	28.5%

Source: Sponsor's Submission, Vol. 15.26, pg. 87 (3/06/00).

Table 11 presents the p-values for comparing Clindoxyl to benzoyl peroxide, clindamycin, and vehicle. The p-values are based on an ANOVA model with the effects of treatment, center, and treatment by center interaction. All three comparisons for percent reduction in inflammatory lesions are significant at the 0.05 level for Study 158. The p-values for global improvement comparing the percentage of subjects with 'good' to 'excellent' improvement on each treatment are also presented in Table 11. All three comparisons for global improvement are significant at the 0.05 level for Study 158. Thus, Study 158 supports the efficacy of Clindoxyl for inflammatory lesions.

Table 11 – Treatment Effect P-values for Percent Reduction in Inflammatory Lesions from Baseline to Week 11 and Success in Global Improvement in Study 158 (ITT/LOCF)

Study 158	<i>Inflammatory Lesions p-value</i>	<i>Global Improvement p-value</i>
Clindoxyl vs. Vehicle	<0.001	0.001
Clindoxyl vs. Benzoyl Per.	0.008	0.042
Clindoxyl vs. Clindamycin	<0.001	0.001

Source: Sponsor's Submission, Vol. 15.26, pg. 123 and 262 (3/06/00).

2.3.4 Efficacy Results for Non-Inflammatory Lesions and Total Lesions

For completeness, treatment effect p-values for percent reduction in all lesion types (non-inflammatory, inflammatory and total) are presented in Table 12. Previous reviews of the 5 studies concluded that there was insufficient evidence to support the full indication of acne, primarily because Clindoxyl failed to consistently demonstrate superiority to benzoyl peroxide for non-inflammatory lesions. The only study with a significant result for Clindoxyl versus benzoyl peroxide for percent reduction in non-inflammatory lesions was Study 156 with $p = 0.048$. This significant result for non-inflammatory lesions in Study 156 was paired with a highly non-significant result for inflammatory lesions for Clindoxyl versus benzoyl peroxide ($p=0.845$). For the full indication of acne, the sponsor must demonstrate statistical significance for two out of three types of lesions. Only one

study meets these criteria (Study 150) for all comparisons with Clindoxyl, and Study 150 is the smallest study, with only 30 patients per arm, conducted at a single center. Since the sponsor has not adequately demonstrated that Clindoxyl is superior to its components for two out of three types of lesions, the full acne indication is not warranted. However, the sponsor has demonstrated more consistent results for inflammatory lesions, with significant results for all comparisons in 3 studies.

Table 12 – Treatment Effect P-values for Percent Reduction in Non-Inflammatory, Inflammatory and Total Lesions from Baseline to Week 11 (ITT/LOCF)

Study 150 (N=120)	Non.	Infl.	Total
Clindoxyl vs. Vehicle	0.001	<0.001	<0.001
Clindoxyl vs. Benzoyl Per.	0.180	0.017	0.030
Clindoxyl vs. Clindamycin	0.005	0.010	0.002

Study 151 (N=273)	Non.	Infl.	Total
Clindoxyl vs. Vehicle	<0.001	<0.001	<0.001
Clindoxyl vs. Benzoyl Per.	0.345	0.002	0.058
Clindoxyl vs. Clindamycin	0.001	<0.001	<0.001

Study 152 (N=280)	Non.	Infl.	Total
Clindoxyl vs. Vehicle	0.130	0.078	0.046
Clindoxyl vs. Benzoyl Per.	0.053	0.082	0.040
Clindoxyl vs. Clindamycin	0.010	0.474	0.025

Study 156 (N=288)	Non.	Infl.	Total
Clindoxyl vs. Benzoyl Per.	0.048	0.845	0.080
Clindoxyl vs. Clindamycin	<0.001	0.030	<0.001

Study 158 (N=358)	Non.	Infl.	Total
Clindoxyl vs. Vehicle	0.001	<0.001	<0.001
Clindoxyl vs. Benzoyl Per.	0.633	0.008	0.109
Clindoxyl vs. Clindamycin	0.316	<0.001	0.005

p-values based on ANOVA.

Source: Sponsor's Submission, Vol. 36.4, pg. 3 – 5 (2/26/02) and Statistical Review, NDA 50-741, 7/17/00

2.4 Statistical Evaluation of Collective Evidence

The sponsor has conducted 5 studies with Clindoxyl, one single center study and four multi-center studies. For percent reduction in inflammatory lesions, 3 out of 5 studies (Studies 150, 151, and 158) were statistically significant for the comparisons of Clindoxyl versus vehicle, benzoyl peroxide, and clindamycin (largest p-value for the 9 comparisons was 0.0169). Of the remaining two studies, Study 156 (which did not have a vehicle arm) demonstrated the superiority of Clindoxyl to clindamycin, but not to benzoyl peroxide. The remaining study, Study 152, failed to demonstrate the statistical superiority of Clindoxyl to any of the other arms, although the comparisons between

Clindoxyl and benzoyl peroxide, and Clindoxyl and vehicle trended in the direction favoring Clindoxyl. Thus, for percent reduction in inflammatory lesions, 3 studies have demonstrated the statistical superiority of Clindoxyl to its components, and 2 studies lack statistical significance.

For the assessment of global improvement, the same 3 studies (150, 151, and 158) were statistically significant for the comparisons of Clindoxyl versus vehicle, benzoyl peroxide, and clindamycin (largest p-value for the 9 comparisons was 0.042). Neither Study 152 nor 156 statistically demonstrated the superiority of Clindamycin to vehicle, benzoyl peroxide, or clindamycin for the global improvement variable.

2.5 Conclusions and Recommendations

The superiority of Clindoxyl versus benzoyl peroxide, clindamycin, and vehicle for the percent reduction in inflammatory lesions and global improvement was demonstrated in Studies 150, 151, and 158. Study 152 did not demonstrate statistical significance between Clindoxyl and benzoyl peroxide, clindamycin, or vehicle for either percent reduction in inflammatory lesions or global improvement. Study 156 demonstrated the statistical superiority of Clindoxyl to clindamycin but not benzoyl peroxide in terms of percent reduction in inflammatory lesions. Also for Study 156, the comparisons between Clindoxyl and benzoyl peroxide and clindamycin were not significant in terms of global improvement. With three positive studies, the sponsor has submitted sufficient information to statistically support a limited indication for the treatment of inflammatory lesions.

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